A 65-year-old man comes to the office for follow-up monitoring of type 2 diabetes mellitus. He was diagnosed with diabetes 7 years ago and follows a strict diet to control his blood sugar level. The patient takes no medications. Blood pressure is 139/88 mm Hg and pulse is 70/min. Physical examination shows decreased lower-extremity sensation with a 10-g monofilament. His most recent hemoglobin A1c is 7.4% (normal, <5.6%). Serum creatinine is 1.0 mg/dL and serum potassium is 3.8 mEq/L. Further laboratory evaluation reveals increased urinary albumin excretion, but a conventional urinalysis is within normal limits. In addition to starting antihyperglycemic treatment, which of the following is the best pharmacotherapy for this patient?

- A. Amlodipine
- B. Carvedilol
- C. Eplerenone
- D. Hydrochlorothiazide
- E. Isosorbide dinitrate
- F. Lisinopril
- G. Terazosin

Submit

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- A. Amlodipine (1%)
- ✗ B. Carvedilol (1%)
- C. Eplerenone (7%)
- D. Hydrochlorothiazide (6%)
- E. Isosorbide dinitrate (0%)
- ✓ F. Lisinopril (80%)
- G. Terazosin (0%)

Incorrect
Correct answer
F

80%
Answered correctly

24 secs
Time Spent

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Explanation

Natural history of diabetic nephropathy

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F. Lisinopril (80%)

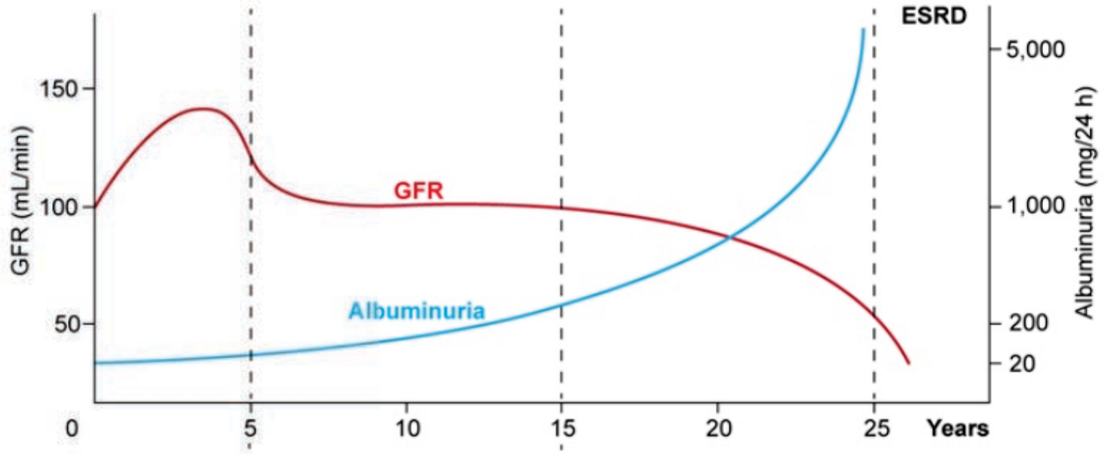
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Incorrect
Correct answer
F

Explanation

Exhibit Display

Natural history of diabetic nephropathy



Hyperfiltration
- Glomerular hypertrophy
- ↑ GFR

Incipient DN
- Mesangial expansion, glomerular basement membrane thickening, arteriolar hyalinosis
- Moderately increased albuminuria
- Hypertension

Overt DN
- Mesangial nodules (Kimmelstiel-Wilson lesion), tubulointerstitial fibrosis
- Overt proteinuria
- Nephrotic syndrome
- ↓ GFR

DN = diabetic nephropathy; **ESRD** = end-stage renal disease; **GFR** = glomerular filtration rate.
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This patient has diabetes mellitus complicated by neuropathy (decreased lower-extremity sensation) and nephropathy (increased urinary albumin excretion). **Moderately increased albuminuria** (also called microalbuminuria) is defined as urine albumin loss of 30-300 mg/day and is an early indication of **diabetic nephropathy** (DN). Microalbuminuria cannot be detected by standard dipstick urinalysis; only albumin excretion >300 mg/day (severely increased albuminuria) can be detected by conventional urinalysis. If left untreated, albuminuria is followed by progressive worsening of renal function leading to end-stage renal disease.

The progression of DN can be reduced by **glycemic and blood pressure control**. In addition, progression can be slowed by use of **ACE inhibitors** (eg, lisinopril) or angiotensin II receptor blockers. Early DN is characterized by elevated glomerular filtration pressure; angiotensin II further increases glomerular pressure by selective vasoconstriction of the efferent arteriole. Blockade of this angiotensin effect **lowers glomerular pressure**. Although ACE inhibitors decrease glomerular filtration in the short term, chronic use decreases albumin excretion and slows progression to overt renal failure. This benefit is independent of effects on systemic blood pressure and can also be seen in nonhypertensive patients.

(Choice A) Nondihydropyridine calcium channel blockers (eg, diltiazem, verapamil) decrease proteinuria, but this effect is not seen with dihydropyridine agents (eg, amlodipine, nifedipine). Although blood pressure control is important in patients with diabetes, lisinopril is more beneficial for preventing progression of nephropathy.

(Choices B and C) Carvedilol is a nonselective beta- and alpha-adrenergic blocker used in hypertension and congestive heart failure. Eplerenone is a mineralocorticoid (aldosterone) antagonist that is also used in congestive heart failure. These agents have no specific role in the management of DN.

(Choice D) Hydrochlorothiazide is an effective antihypertensive agent. However, it also causes hyperglycemia and may be associated with worsened glucose control in diabetic patients. ACE inhibitors are preferred over thiazides for first-line treatment.

(Choice E) Isosorbide dinitrate is an intermediate-acting nitrate used in the treatment of stable angina pectoris. It has no role in the management of DN.

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(Choice E) Isosorbide dinitrate is an intermediate-acting nitrate used in the treatment of stable angina pectoris. It has no role in the management of DN.

(Choice G) Alpha-1 blockers (eg, doxazosin, prazosin, terazosin) are useful for treatment of hypertension and benign prostatic hyperplasia but are not recommended as monotherapy for hypertension due to an increased risk of cardiovascular events.

Educational objective:
The risk of progression of diabetic nephropathy in patients with proteinuria can be reduced by appropriate glycemic and blood pressure control. ACE inhibitors and angiotensin II receptor blockers are the preferred antihypertensive agents due to their antiproteinuric effects, which are independent from their effects on systemic blood pressure.

References

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A 7-year-old boy is brought to the clinic by his parents after he developed red urine earlier in the day. The patient has a history of atopic dermatitis. He had a skin infection one month ago that was treated with a short course of antibiotics. Blood pressure is 140/90 mm Hg. On physical examination, there is periorbital edema, as well as pitting edema on both feet. Laboratory results are as follows:

Serum chemistry	
Blood urea nitrogen	14 mg/dL
Creatinine	1.4 mg/dL

Which of the following is most likely responsible for this patient's renal injury?

- A. $CD8^+$ T lymphocytes
- B. Histamine release
- C. IgG autoantibodies
- D. IgG immune complexes
- E. Macrophages

Submit

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Incorrect
Correct answer
D

Collecting Statistics

44 secs
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Explanation

Hypersensitivity reactions

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Hypersensitivity reactions			
	Humoral components	**Cellular components**	**Examples**
Type I (immediate)	• **IgE**	• Basophils • Mast cells	• Anaphylaxis • Allergies
Type II (cytotoxic)	• **IgG & IgM** autoantibodies • Complement activation	• NK cells • Eosinophils • Neutrophils • Macrophages	• Autoimmune hemolytic anemia • Goodpasture syndrome
Type III (immune complex)	• Deposition of **antibody-antigen complexes** • Complement activation	• Neutrophils	• Serum sickness • PSGN • Lupus nephritis
Type IV (delayed type)	• None	• **T cells** • **Macrophages**	• Contact dermatitis • Tuberculin skin test

NK = natural killer; **PSGN** = poststreptococcal glomerulonephritis.

This patient with atopic dermatitis is predisposed to secondary skin infections (eg, impetigo, cellulitis). His

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This patient with atopic dermatitis is predisposed to secondary skin infections (eg, impetigo, cellulitis). His **antecedent skin infection**, along with overt nephritic syndrome (eg, hypertension, generalized edema, **gross hematuria** [cola- or red-colored urine]) is suggestive of **poststreptococcal glomerulonephritis** (PSGN). This disease is the most common cause of acute nephritis in children and typically manifests 2-4 weeks after a skin infection.

During infection, IgG antibodies form against nephritogenic antigens expressed by certain strains of group A *Streptococcus*. These antibodies complex with streptococcal antigens to form **immune complexes** that are deposited along the glomerular basement membrane (**type III hypersensitivity**). Subsequent activation of the complement cascade leads to neutrophil recruitment and inflammatory damage to the glomeruli.

(Choices A and E) Cytotoxic $CD8^+$ T lymphocytes and macrophages play a prominent role in type IV (delayed-type) hypersensitivity reactions. These cells are stimulated by T-helper cells, leading to localized inflammation, cellular destruction, and (often) granuloma formation. Although certain forms of acute interstitial nephritis are due to type IV hypersensitivity, gross hematuria is uncommon and affected patients classically present with fever, rash, and eosinophilia.

(Choice B) Histamine is released by mast cells and basophils during type I (immediate) hypersensitivity, which is seen with anaphylaxis and allergies, not PSGN. Mast cells and basophils are coated by IgE molecules, which cross-link on antigen exposure, triggering the release of histamine and other mediators.

(Choice C) Direct binding of autoantibodies to tissue is responsible for type II (cytotoxic) hypersensitivity reactions. This underlies Goodpasture syndrome (antibodies directed at type IV collagen), which can cause generalized edema (glomerulonephritis) and hemoptysis (diffuse alveolar hemorrhage). However, PSGN is a much more common cause of glomerulonephritis in children.

Educational objective:
Poststreptococcal glomerulonephritis is the most common cause of nephritic syndrome (eg, hematuria, edema, hypertension) in children, typically occurring 2-4 weeks after a streptococcal skin infection (eg, impetigo, cellulitis).

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Educational objective:
Poststreptococcal glomerulonephritis is the most common cause of nephritic syndrome (eg, hematuria, edema, hypertension) in children, typically occurring 2-4 weeks after a streptococcal skin infection (eg, impetigo, cellulitis). It is caused by a type III (immune complex–mediated) hypersensitivity reaction.

Immunology Renal, Urinary Systems & Electrolytes Poststreptococcal Glomerulonephritis

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(immune complexes

Exhibit Display

Nephritic vs nephrotic syndrome		
	Nephritic	**Nephrotic**
Proteinuria	Mild	Significant (>3.5 g/day)
Serum albumin	Normal	Decreased
Edema	Mild	Significant
GFR	Decreased	Normal
Hypertension	Yes	No
Hematuria	Yes	No
Pyuria	Yes	No
Casts	RBC	Fatty or none

GFR = glomerular filtration rate; **RBC** = red blood cell.

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(Choice B) Histamine is released by mast cells and basophils during type I (immediate) hypersensitivity, which is

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A 68-year-old man comes to the emergency department due to abdominal pain and nausea for the past 2 days. He has a history of atherosclerotic cardiovascular disease and underwent coronary artery bypass surgery 2 years ago. Blood pressure is 105/65 mm Hg and heart rate is 120/min and irregular. Abdominal examination reveals mild diffuse tenderness and decreased bowel sounds. Laboratory studies are as follows:

Serum chemistry	
Sodium	142 mEq/L
Chloride	104 mEq/L
Bicarbonate	12 mEq/L
Creatinine	0.8 mg/dL
Arterial blood gases	
pH	7.25
$PaCO_2$	29 mm Hg
Lactic acid, venous blood	5.6 mmol/L (normal: 0.5 - 2.0 mmol/L)

ECG shows absent P waves and an irregular rate and rhythm. CT scan of the abdomen reveals colonic wall thickening and no enhancement with intravenous contrast. Urinalysis shows acidic urine. Renal metabolism of which of the following amino acids is most important for maximizing acid excretion in this patient?

- A. Alanine
- B. Arginine
- C. Aspartate
- D. Glutamine

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- D. Glutamine
- E. Histidine

Submit

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ECG shows absent P waves and an irregular rate and rhythm. CT scan of the abdomen reveals colonic wall thickening and no enhancement with intravenous contrast. Urinalysis shows acidic urine. Renal metabolism of which of the following amino acids is most important for maximizing acid excretion in this patient?

- ✗ A. Alanine (10%)
- B. Arginine (22%)
- C. Aspartate (22%)
- ✓ D. Glutamine (36%)
- E. Histidine (6%)

Incorrect
Correct answer
D

36%
Answered correctly

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Time Spent

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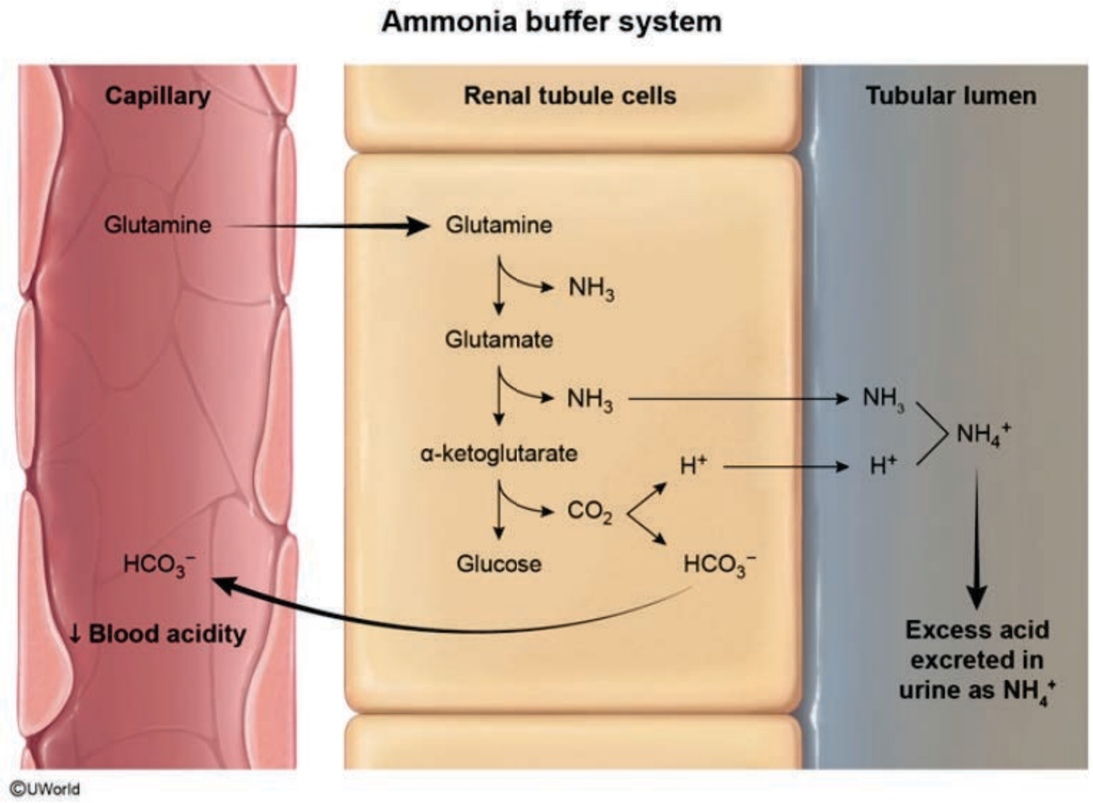
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Correct answer
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36%
Answered correctly

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The
anion gap metabolic acidosis. Acidosis stimulates **renal ammoniagenesis**, a process by which renal epithelial

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This patient has **acute ischemic colitis**, which is most likely due to embolic disease related to his atrial fibrillation. The ischemic bowel undergoes anaerobic metabolism, causing **lactate accumulation** in the blood that leads to an anion gap metabolic acidosis. Acidosis stimulates **renal ammoniagenesis**, a process by which renal epithelial cells metabolize **glutamine**, generating ammonium and bicarbonate. Ammonium ions are transported into the tubular fluid and excreted in the urine while peritubular capillaries absorb bicarbonate, which functions to buffer acids in the blood.

Under normal physiologic conditions, about half of the total amount of acid secreted in the urine is in the form of ammonium, and the remainder is excreted primarily as titratable acids, particularly inorganic phosphate. However, **increased ammonium production** is almost entirely responsible for the increase in renal acid excretion seen with **chronic acidosis**.

(Choices A and C) Alanine and aspartate are glucogenic amino acids. Alanine is metabolized in the liver to produce pyruvate and aspartate can be readily interconverted with oxaloacetate.

(Choice B) Arginine is a urea cycle intermediate that helps to remove nitrogenous waste products (eg, ammonium) from the blood. Hepatic metabolism of arginine results in the production of urea and ornithine.

(Choice E) Histidine, an essential amino acid, is converted to histamine by histidine decarboxylase. Histamine is involved in the acute inflammatory response and gastric acid secretion; it also functions as a neurotransmitter.

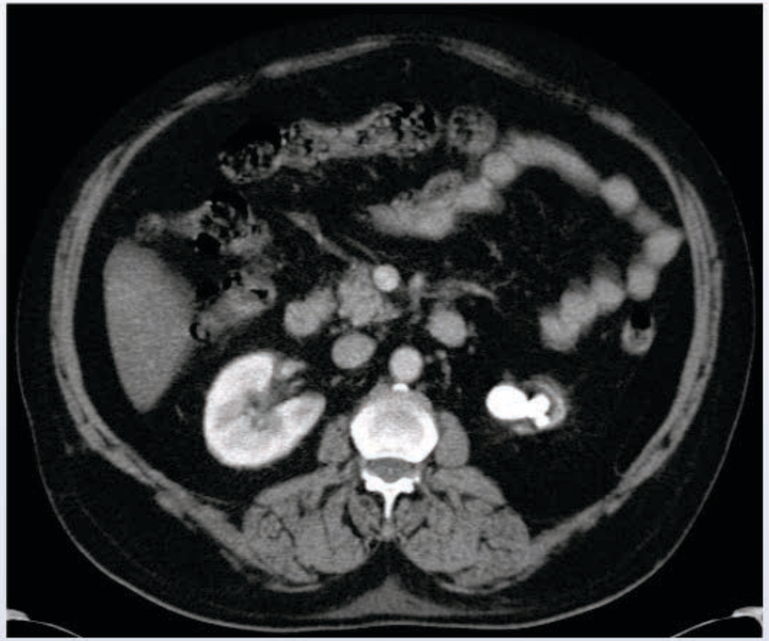
Educational objective:
Acidosis stimulates renal ammoniagenesis, a process by which renal tubular epithelial cells metabolize glutamine to glutamate, generating ammonium that is excreted in the urine and bicarbonate that is absorbed into the blood. This process is responsible for the vast majority of renal acid excretion in chronic acidotic states.

References

- Renal ammonia metabolism and transport.

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A 60-year-old woman comes to the emergency department due to left flank pain and hematuria. Medical history is significant for recurrent urinary tract infections and hypothyroidism. Blood pressure is 130/80 mm Hg and pulse is 80/min. Physical examination shows left flank tenderness. CT scan of the abdomen is shown below:



Urinalysis for this patient would most likely show which of the following?

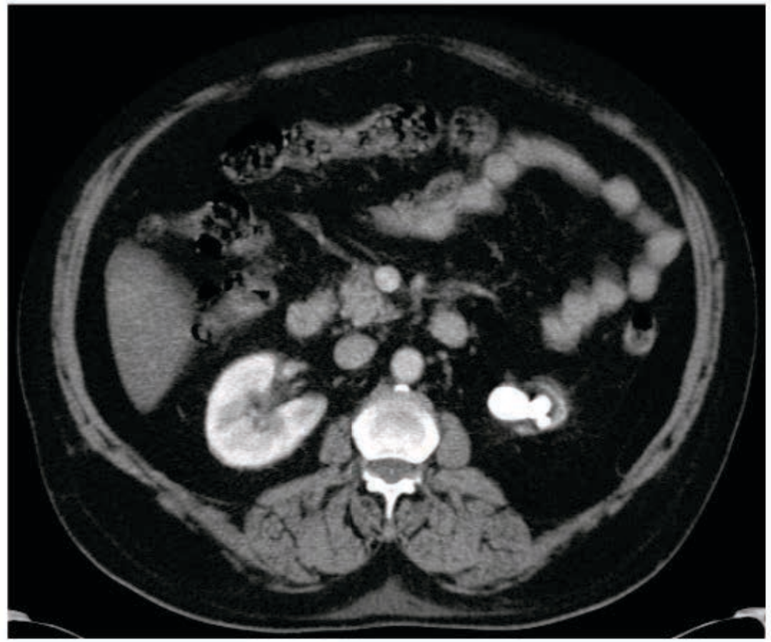
- A. 4+ protein
- B. Numerous eosinophils
- C. pH 8.0
- D. Red blood cell casts
- E. Specific gravity 1.002

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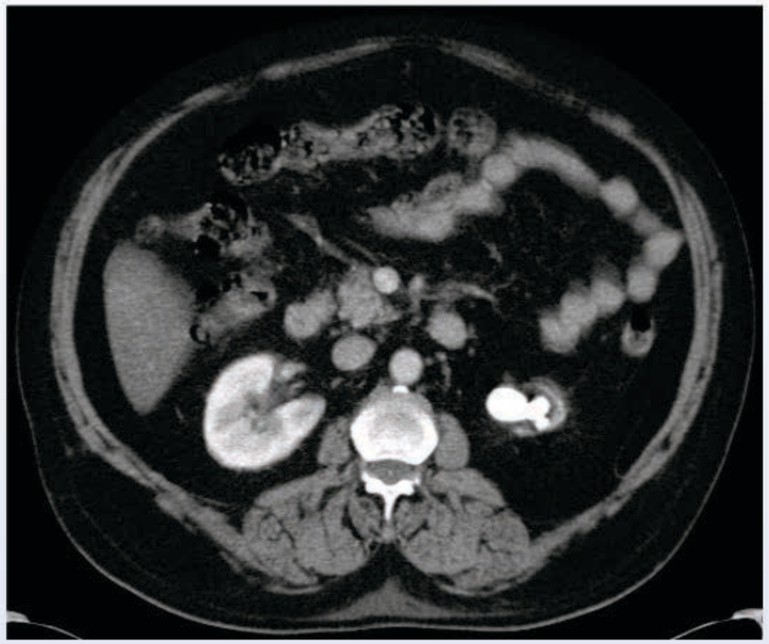


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E. Specific gravity 1.002

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80/min. Physical examination shows left flank tenderness. CT scan of the abdomen is shown below:



Urinalysis for this patient would most likely show which of the following?

- A. 4+ protein
- B. Numerous eosinophils
- C. pH 8.0
- D. Red blood cell casts
- E. Specific gravity 1.002
- F. Uric acid crystals

Submit

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Urinalysis for this patient would most likely show which of the following?

- A. 4+ protein (4%)
- B. Numerous eosinophils (3%)
- ✓ C. pH 8.0 (50%)
- D. Red blood cell casts (21%)
- E. Specific gravity 1.002 (4%)
- F. Uric acid crystals (15%)

Correct

50%
Answered correctly

19 secs
Time Spent

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Struvite (magnesium ammonium phosphate) stones	
Risk factors	• Recurrent upper urinary tract infection • Urease-producing organisms (eg, *Klebsiella*, *Proteus*)
Pathogenesis	• Hydrolysis of urea to yield ammonia: $\text{Urea} \rightarrow 2\ NH_3 + CO_2$ $NH_3 + H_2O \rightarrow NH_4^+ + OH^-$ • Increased urine pH • Precipitation of magnesium ammonium phosphate salts
Clinical features	• Large staghorn calculi • Fever, mild flank pain due to infection • Obstruction of collecting system & atrophy of renal parenchyma

This patient's imaging shows an atrophic left kidney associated with a large, hyperdense mass filling the renal pelvis. These findings are consistent with a chronic staghorn calculus, a type of kidney stone that occurs in patients with recurrent upper urinary tract infection caused by **urease-producing organisms** (eg, *Proteus*, *Klebsiella*). Hydrolysis of urea yields **ammonia**, which **alkalinizes the urine** (ie, pH >7) and facilitates precipitation of struvite crystals (magnesium ammonium phosphate).

Because of the large quantities of urea excreted in urine, struvite stones can **grow rapidly** into a branched staghorn calculus that **fills the renal calyces and pelvis**. Symptoms are usually related to the underlying infection (eg, fever, mild costovertebral pain, hematuria); renal colic (ie, severe flank/groin pain) is uncommon because large stones are unable to pass into the ureter and cause acute obstruction. Over time, the affected **kidney can atrophy** due to recurrent infection and chronic obstructive nephropathy.

(Choice A) Trace or weakly positive (eg, 1 or 2+) proteinuria can be seen in a variety of disorders (eg, hematuria

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(Choice A) Trace or weakly positive (eg, 1 or 2+) proteinuria can be seen in a variety of disorders (eg, hematuria due to kidney stones, urinary tract infection) due to disruption of the urothelium; however, a strongly positive result (eg, 3 or 4+) is more specific for glomerular protein loss (eg, amyloidosis, diabetic nephropathy) and is not usually due to stones.

(Choice B) Eosinophiluria is typically associated with acute interstitial nephritis, which is most commonly triggered by exposure to certain medications (eg, beta-lactam antibiotics, nonsteroidal anti-inflammatory drugs). Patients typically have a rash, fever, and acute kidney injury, but this condition is not associated with staghorn calculi.

(Choice D) Red cell casts and dysmorphic red blood cells form when erythrocytes traverse the renal tubules and indicate a glomerular bleeding source (eg, glomerulonephritis). Staghorn calculi can cause hematuria with morphologically normal red cells due to irritation of the urothelium, but do not cause glomerular bleeding.

(Choice E) Urine specific gravity correlates with urine concentration and is influenced by hydration status and regulatory hormone (eg, antidiuretic hormone) levels. Kidney stones most commonly form in concentrated urine (eg, >1.015), which results in supersaturation of salts and crystal precipitation. A specific gravity of ≤1.003 indicates dilute urine, and it is unlikely that a patient with an acute stone would have such a low specific gravity.

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(Choice F) Uric acid stones can occasionally form staghorn calculi but would typically be seen in patients with gout or conditions with rapid cell turnover (eg, myeloproliferative disorders) rather than recurrent urinary tract infection. This patient is much more likely to have a struvite stone.

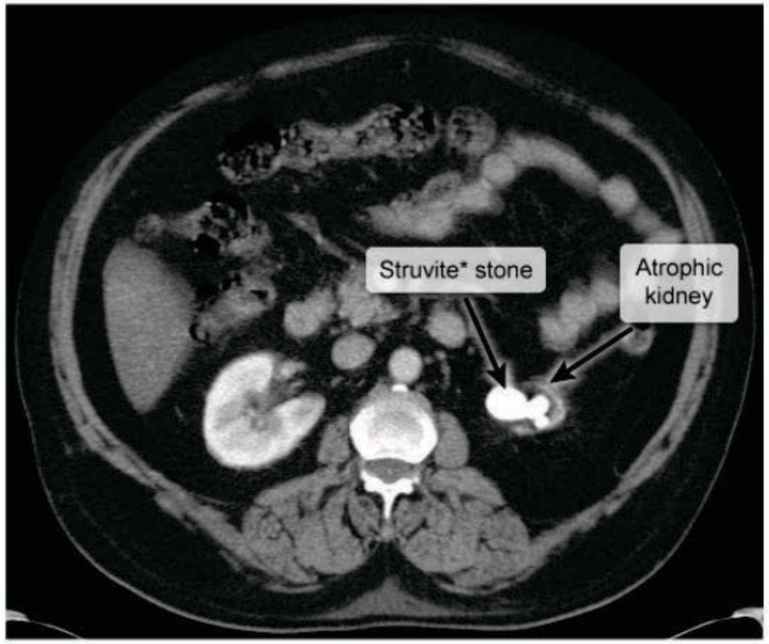
Educational objective:
Struvite stones are typically seen in patients with recurrent upper urinary infection by urease-producing organisms (eg, *Proteus*, *Klebsiella*). Hydrolysis of urea yields ammonia, which alkalinizes the urine and facilitates precipitation of magnesium ammonium phosphate. Urinalysis shows hematuria and elevated urine pH.

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• Precipitation of magnesium ammonium phosphate salts

Exhibit Display

Staghorn calculus



*Magnesium ammonium phosphate precipitates in alkaline (pH >7) urine

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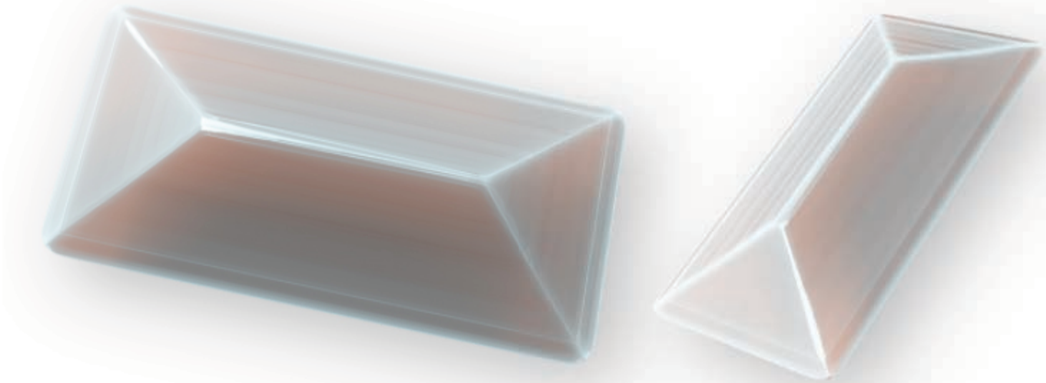
morphologically normal red cells due to irritation of the urothelium, but do not cause glomerular bleeding.

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- Precipitation of magnesium ammonium phosphate salts

Exhibit Display

Triple phosphate
(magnesium ammonium phosphate)



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morphologically normal red cells due to irritation of the urothelium, but do not cause glomerular bleeding.

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A 70-year-old man is brought to the hospital by his son for evaluation of worsening fatigue. The patient has not seen a physician in the past 15 years. He takes naproxen occasionally for knee arthritis. Physical examination of the prostate shows no abnormalities. Laboratory results are as follows:

Complete blood count	
Hemoglobin	10.5 g/dL
Leukocytes	7,100/mm^3
Platelets	150,000/mm^3
Serum chemistry	
Sodium	135 mEq/L
Potassium	5.1 mEq/L
Blood urea nitrogen	45 mg/dL
Creatinine	3.0 mg/dL

Urine sediment is unremarkable. Ultrasound examination shows bilateral small kidneys and no hydronephrosis. Kidney biopsy shows intimal thickening and luminal narrowing of the renal arterioles with evidence of glomerular sclerosis. Which of the following is most likely responsible for this patient's kidney disease?

- A. Analgesic use
- B. Fibromuscular dysplasia
- C. Hepatitis C infection
- D. Hypertension

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- B. Fibromuscular dysplasia
- C. Hepatitis C infection
- D. Hypertension
- E. Multiple myeloma

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- ✗ A. Analgesic use (21%)
- B. Fibromuscular dysplasia (6%)
- C. Hepatitis C infection (3%)
- ✓ D. Hypertension (64%)
- E. Multiple myeloma (4%)

Incorrect
Correct answer
D

64%
Answered correctly

13 secs
Time Spent

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This patient's biopsy findings are consistent with **hypertensive nephrosclerosis** (HN), a complication of chronic hypertension that is most common in elderly patients. Prolonged elevation of systemic blood pressure causes the renal arterioles to undergo compensatory **medial hypertrophy** and **fibrointimal proliferation**. Endothelial damage leads to deposition of plasma proteins and basement membrane material in the arteriolar walls (**hyaline arteriolosclerosis**). The resultant lumenal narrowing restricts renal blood flow, resulting in glomerular ischemia and fibrosis (**glomerulosclerosis**) with collapse of the capillary loops and thickening of the Bowman capsule. Gross examination of affected kidneys shows mild **renal atrophy** with a finely granular surface.

HN generally progresses slowly, and most patients with mild to moderate disease do not develop renal insufficiency. However, advanced disease occurs more commonly in patients of African American descent and in those with severe hypertension or comorbid diabetes. Proteinuria is common in advanced disease, but **urinalysis** is otherwise typically **bland** (eg, no casts, red or white blood cells). Like all chronic kidney diseases, advanced HN can cause **anemia** due to a reduction in renal erythropoietin production.

(Choice A) Analgesic nephropathy can occur with prolonged, excessive nonsteroidal anti-inflammatory use. However, pathologic findings typically include papillary necrosis and tubulointerstitial nephritis.

(Choice B) Fibromuscular dysplasia causes renal artery stenosis, resulting in refractory hypertension. However, it typically occurs in younger women (age <50), and histology characteristically shows fibromuscular ridges alternating with areas of aneurysmal dilation affecting the main renal artery.

(Choice C) Hepatitis C infection can cause membranous nephropathy, which presents with nephrotic syndrome (eg, proteinuria, edema). Histology demonstrates diffuse thickening of the glomerular basement membrane without glomerular hypercellularity.

(Choice E) Multiple myeloma can cause anemia and renal disease, but histology typically demonstrates a light chain cast nephropathy; eosinophilic casts obstruct the renal tubules, resulting in tubular inflammation and fibrosis. Patients typically also have fatigue, constipation (hypercalcemia), and bone pain (lytic lesions).

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Educational objective:
Chronic hypertension can result in hypertensive nephrosclerosis, which is characterized by compensatory medial hypertrophy and fibrointimal proliferation; endothelial damage from elevated systemic pressure also leads to hyaline arteriolosclerosis. The narrowed arteriolar lumens cause a progressive decrease in renal blood flow, resulting in glomerular ischemia and fibrosis (glomerulosclerosis).

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A 1-hour-old boy is in the neonatal intensive care unit due to tachypnea and hypoxia. The infant was born at 39 weeks gestation via cesarean delivery due to recurrent variable decelerations. The pregnancy was complicated by lack of prenatal care. The infant weighs 3.2 kg (7 lb 1 oz). Physical examination shows a flattened nose and bilateral club feet. Breath sounds are markedly diminished bilaterally. The infant is intubated and mechanically ventilated, but oxygen levels do not improve. He dies an hour later. Which of the following is most likely to be found during autopsy of this infant?

- A. Congenital diaphragmatic hernia
- B. Duodenal atresia
- C. Renal agenesis
- D. Surfactant deficiency
- E. Tracheoesophageal fistula

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- A. Congenital diaphragmatic hernia (5%)
- ✗ B. Duodenal atresia (2%)
- ✓ C. Renal agenesis (75%)
- D. Surfactant deficiency (9%)
- E. Tracheoesophageal fistula (7%)

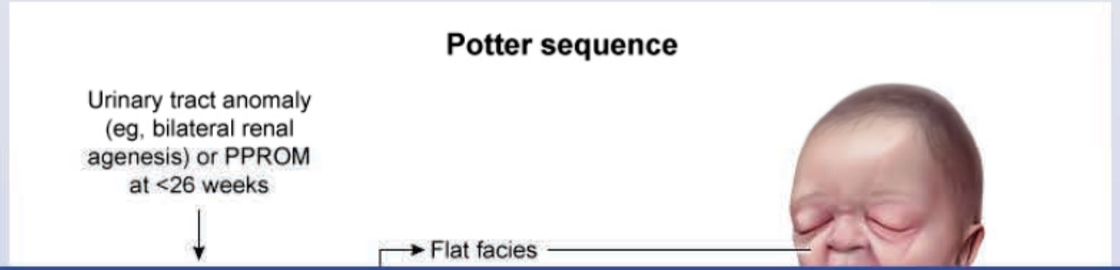
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Correct answer
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75%
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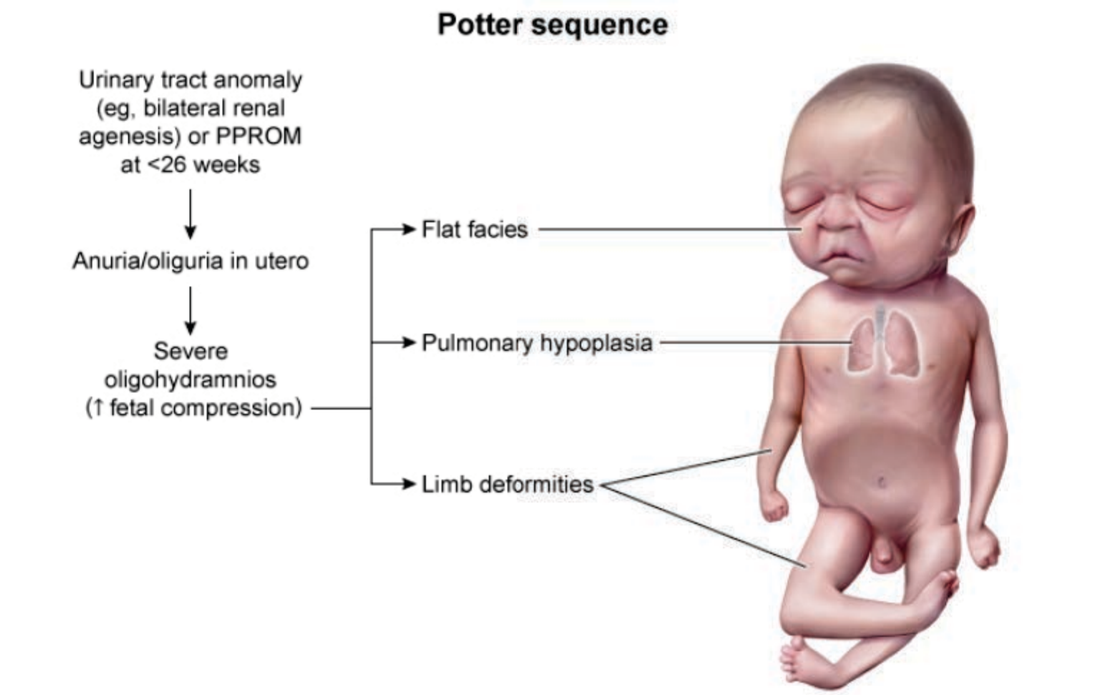
Explanation



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E. Tracheoesophageal fistula (7%)

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This infant likely had **Potter sequence**, which is characterized by pulmonary hypoplasia, flat facies, and lower limb deformity (eg, club foot). Potter sequence is caused by a **urinary tract anomaly** that leads to **decreased fetal**

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This infant likely had **Potter sequence**, which is characterized by pulmonary hypoplasia, flat facies, and lower limb deformity (eg, club foot). Potter sequence is caused by a **urinary tract anomaly** that leads to **decreased fetal urine output**. It is classically associated with bilateral renal agenesis but can occur secondary to other etiologies, including posterior urethral valves or fetal exposure to ACE inhibitors.

Because fetal urine is the main component of amniotic fluid, decreased fetal urine output can lead to low or absent amniotic fluid levels (ie, **severe oligohydramnios**). Inadequate amniotic fluid levels allow for **increased external compression** of the fetal face (**flat facies**) and extremities (eg, **club foot**). In addition, the umbilical cord is often compressed such that fetal heart rate abnormalities (eg, recurrent decelerations) are common during labor.

Amniotic fluid also provides the fluid and growth factors needed for fetal lung development. Therefore, neonates with Potter sequence have **pulmonary hypoplasia** due to the lack of normal alveolar distension by aspirated amniotic fluid. Both lungs are affected, and **respiratory failure** (ie, hypoxia) is the most common cause of death in affected infants.

(Choice A) Congenital diaphragmatic hernia can cause neonatal hypoxia due to lung compression by the herniated abdominal contents; however, infants typically have unilateral (not bilateral) absent breath sounds. In addition, there is no association with flat facies or limb deformity.

(Choices B and E) Infants with gastrointestinal obstruction proximal to the small bowel (eg, duodenal atresia, tracheoesophageal fistula) may have respiratory distress due to stomach distension and subsequent lung compression. However, these neonates have impaired amniotic fluid swallowing in utero, leading to polyhydramnios.

(Choice D) Surfactant decreases alveolar surface tension, and surfactant deficiency (most commonly associated with prematurity) can cause alveolar collapse and neonatal respiratory distress syndrome. However, surfactant deficiency is not typically associated with flat facies or limb deformity.

Educational objective:
Potter sequence results from a urinary tract anomaly (eg, bilateral renal agenesis) that causes decreased fetal

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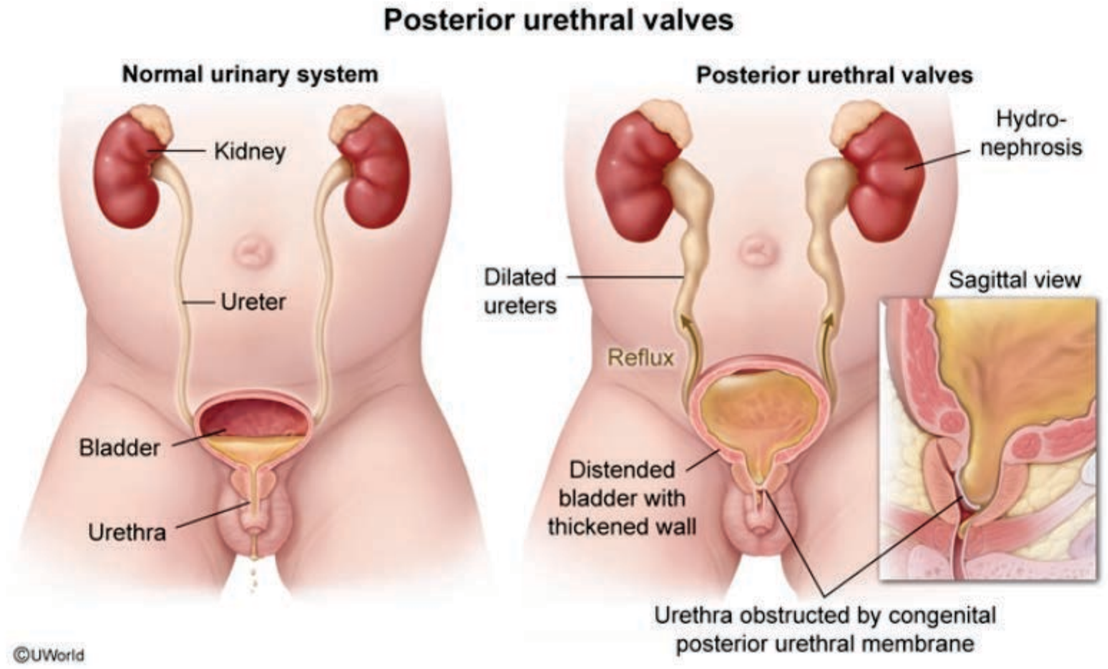
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Educational objective:
Potter sequence results from a urinary tract anomaly (eg, bilateral renal agenesis) that causes decreased fetal urine output and severe oligohydramnios. The lack of amniotic fluid causes increased fetal compression (eg, flat facies, limb deformity) and pulmonary hypoplasia (eg, neonatal hypoxia), which is the most common cause of death in affected neonates.

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Flat facies

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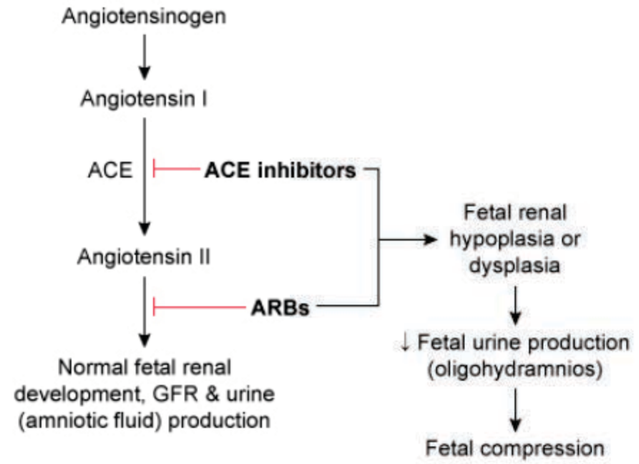
(Choice A) Congenital diaphragmatic hernia can cause neonatal hypoxia due to lung compression by the

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Flat facies

Exhibit Display

Teratogenic effects of ACE inhibitors and ARBs



ARB = angiotensin II receptor blocker; **GFR** = glomerular filtration rate. ©UWorld

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(Choice A) Congenital diaphragmatic hernia can cause neonatal hypoxia due to lung compression by the

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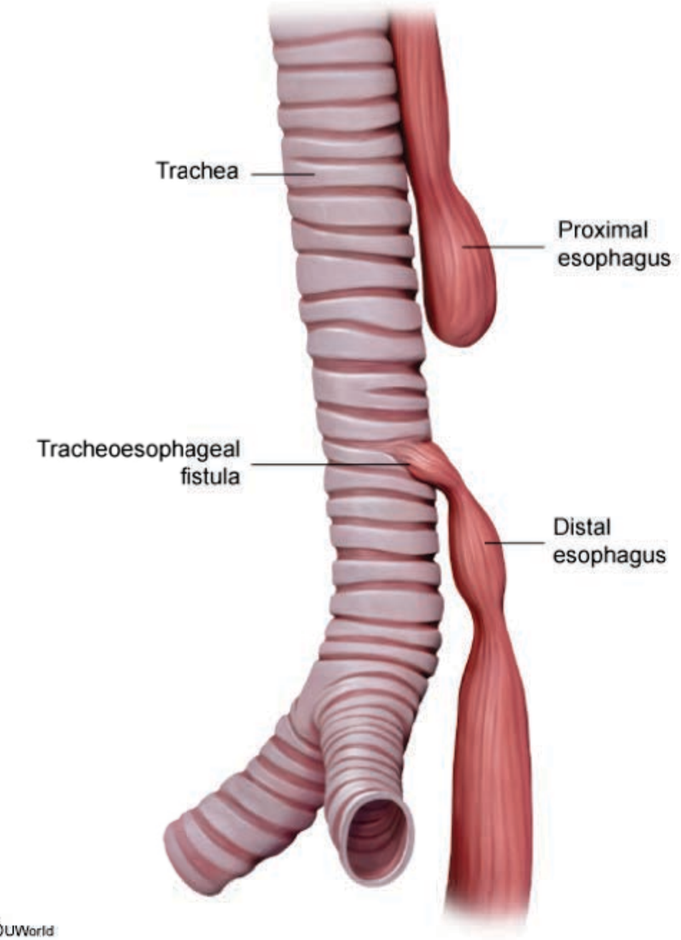
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Esophageal atresia & tracheoesophageal fistula



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A 45-year-old man comes to the office for an annual medical visit. The patient has had prediabetes for the last 2 years. He feels well and takes no medications but has gained weight since his last visit a year ago. The patient has a strong family history of type 2 diabetes mellitus. Blood pressure is 124/78 mm Hg and BMI is 32 kg/m^2. Laboratory results show a fasting blood glucose of 157 mg/dL and serum creatinine of 0.7 mg/dL. Hemoglobin A1c is 7.4%. Urine assay shows no detectable albuminuria. Which of the following renal changes is most likely present in this patient at this time?

- A. Decreased peritubular capillary oncotic pressure
- B. Decreased intraglomerular capillary pressure
- C. Glomerular atrophy
- D. Increased glomerular filtration rate
- E. Increased oncotic pressure in Bowman's space

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- A. Decreased peritubular capillary oncotic pressure (6%)
- ✗ B. Decreased intraglomerular capillary pressure (7%)
- C. Glomerular atrophy (3%)
- ✓ D. Increased glomerular filtration rate (55%)
- E. Increased oncotic pressure in Bowman's space (26%)

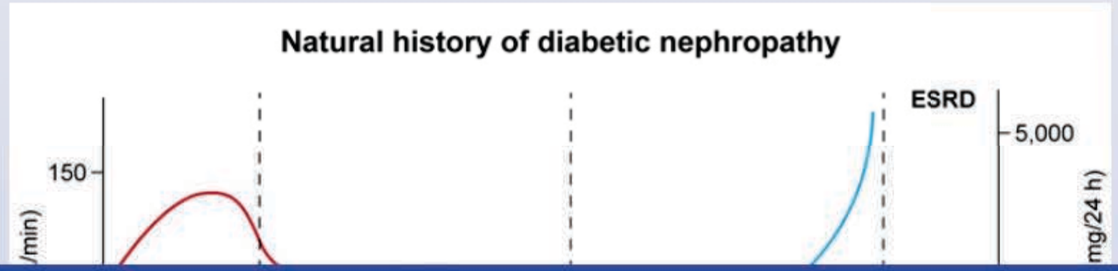
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Correct answer
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Answered correctly

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Explanation



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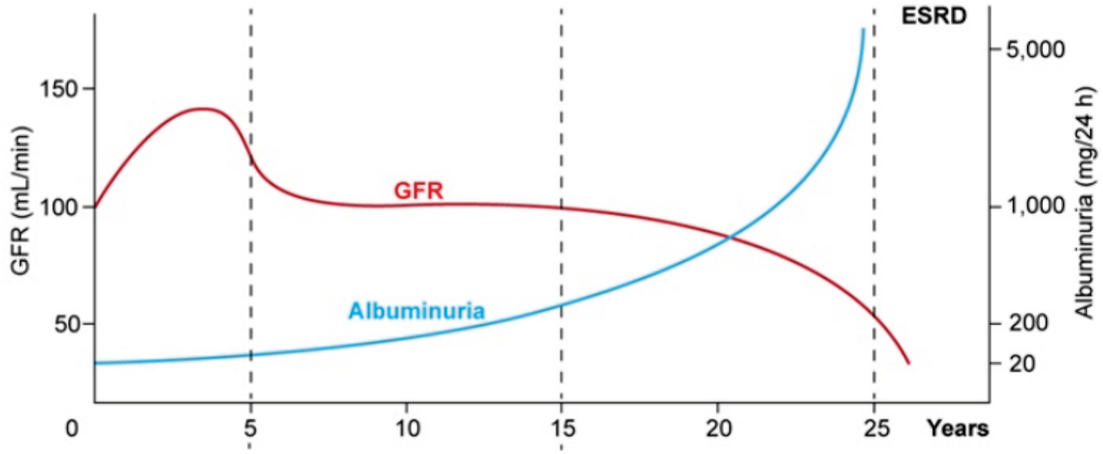
- A. Dec
- B. Dec
- C. Glo
- D. Incr
- E. Incr

Incorrect
Correct answer
D

Explanation

Exhibit Display

Natural history of diabetic nephropathy



Hyperfiltration
- Glomerular hypertrophy
- ↑ GFR

Incipient DN
- Mesangial expansion, glomerular basement membrane thickening, arteriolar hyalinosis
- Moderately increased albuminuria
- Hypertension

Overt DN
- Mesangial nodules (Kimmelstiel-Wilson lesion), tubulointerstitial fibrosis
- Overt proteinuria
- Nephrotic syndrome
- ↓ GFR

DN = diabetic nephropathy; **ESRD** = end-stage renal disease; **GFR** = glomerular filtration rate.
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This patient has type 2 diabetes mellitus, confirmed by elevated blood glucose and hemoglobin A1c. **Diabetic nephropathy** can occur with any form of diabetes mellitus and is the most common cause of end-stage renal disease in the United States.

One of the earliest derangements that contributes to the pathogenesis of diabetic nephropathy is an **increase in the filtered glucose** load. This increases sodium resorption in the proximal tubule by the sodium glucose cotransporter, leading to decreased sodium and fluid delivery to the macula densa and subsequent activation of the tubuloglomerular autoregulation system. Subsequent dilation of the afferent arterioles and constriction of the efferent arterioles increases intraglomerular capillary pressure, resulting in an **increased glomerular filtration rate** (hyperfiltration) and glomerular hypertrophy **(Choices B and C)**.

Although the increased filtration rate appropriately counteracts the excessive sodium reabsorption and prevents fluid retention, over a prolonged period, chronically **elevated intraglomerular capillary pressures** contribute to glomerular structural changes. These include basement membrane thickening, mesangial expansion, and broadening of the podocyte foot processes, which result in the loss of small amounts of albumin in the urine (30-300 mg/day, or moderately increased albuminuria). **Albuminuria** is the earliest clinical sign of diabetic nephropathy and typically occurs before any appreciable rise in serum creatinine. Later in the disease process, there is widespread glomerulosclerosis and a decline in glomerular filtration.

(Choice A) The increased glomerular hydrostatic pressure seen in diabetic nephropathy results in excess water loss in the glomerulus during filtration. The water loss leads to increased concentration of the plasma proteins and increased (rather than decreased) peritubular oncotic pressure.

(Choice E) Increased oncotic pressure in Bowman's space occurs in diabetic nephropathy due to loss of albumin into the ultrafiltrate. However, this patient's urine assay shows no detectable albuminuria, so oncotic pressure would not be increased at this time.

Educational objective:
In diabetic nephropathy, early adaptive changes in the kidney cause a transient increase in glomerular filtration

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Educational objective:
In diabetic nephropathy, early adaptive changes in the kidney cause a transient increase in glomerular filtration (hyperfiltration). As diabetic nephropathy progresses, glomerular filtration falls, with a concurrent increase in urine albumin loss.

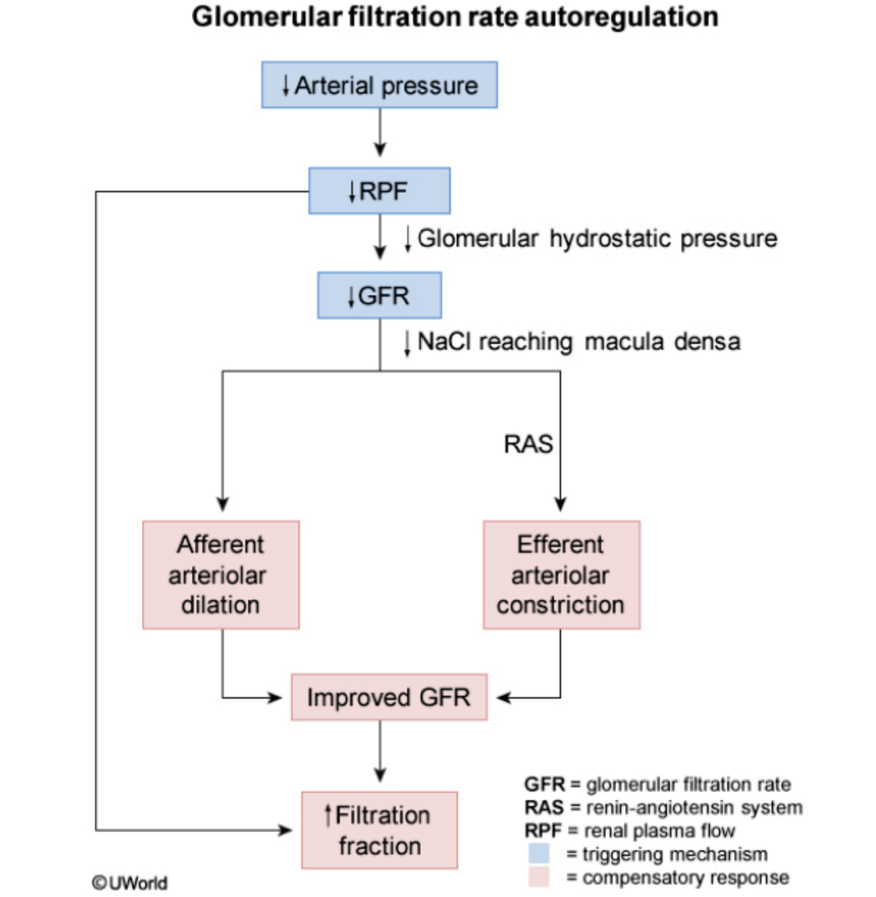
References

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- Moderately increased albuminuria

- Nephrotic syndrome
- ↓ GFR

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A 24-year-old man is being evaluated for gross hematuria. Cystoscopy under general anesthesia is performed. After the scope is passed into the urinary bladder, a triangular portion of the bladder floor formed by the internal urethral orifice and 2 slit-like openings is observed. Gross blood is seen oozing from one of the slit-like openings. Which of the following is the most likely cause of this patient's hematuria?

- A. Bladder rupture
- B. Colovesical fistula
- C. Renal papillary necrosis
- D. Urethral diverticulum
- E. Urinary bladder cancer

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- A. Bladder rupture (12%)
- B. Colovesical fistula (7%)
- ✓ C. Renal papillary necrosis (52%)
- D. Urethral diverticulum (19%)
- E. Urinary bladder cancer (7%)

Correct | 52% Answered correctly | 06 secs Time Spent | 2023 Version

Explanation

Causes of hematuria



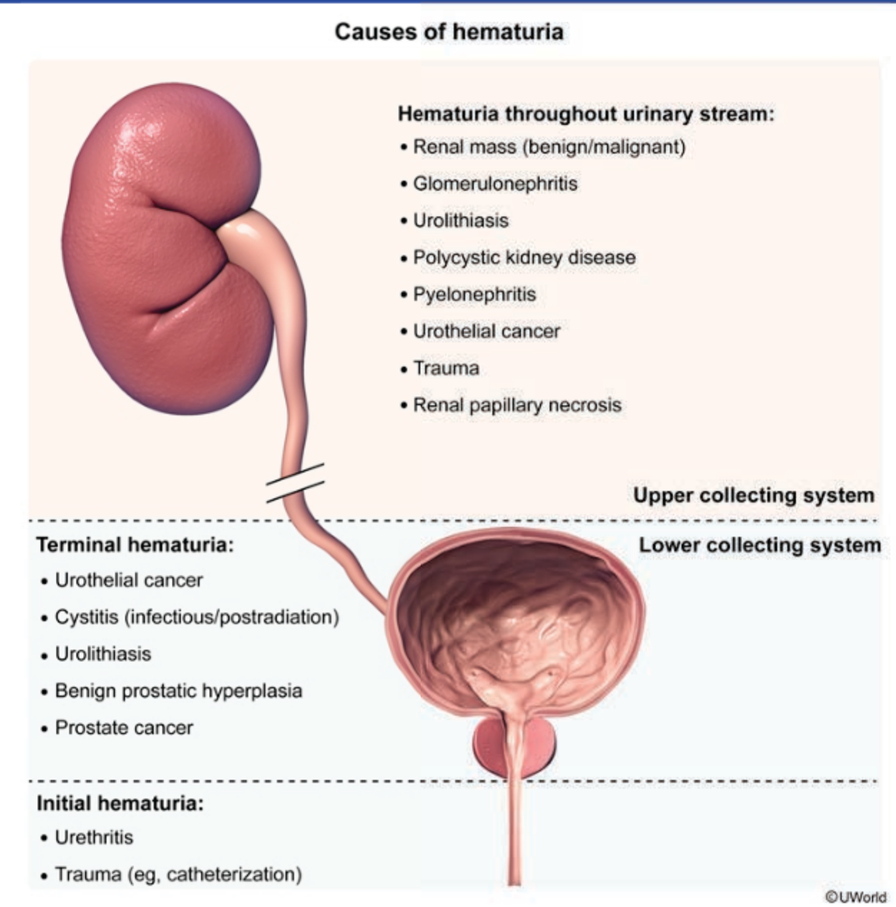
Hematuria throughout urinary stream:

- Renal mass (benign/malignant)
- Glomerulonephritis
- Urolithiasis
- Polycystic kidney disease

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Causes of hematuria

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The trigone is the triangular portion of the **bladder** formed by 2 slit-like **ureteric orifices** and the internal **urethral**

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The trigone is the triangular portion of the **bladder** formed by 2 slit-like **ureteric orifices** and the internal **urethral opening**. Bleeding from the ureter, as seen on this patient's cystoscopy, suggests an origin in the **upper urinary tract** (ie, **kidney or ureter**). In contrast, lower urinary tract bleeding (eg, trauma, infection) originates in the bladder or urethra, and the source is typically directly visualized upon insertion of a cystoscope through the urethra into the bladder.

The etiology of upper urinary tract bleeding is often identified based on other signs and symptoms, such as flank pain suggestive of a ureteral stone. Similarly, associated hypertension or proteinuria may indicate glomerular disease, and fever and pyuria are concerning for pyelonephritis.

In the absence of other findings, **renal papillary necrosis** (RPN) should also be considered as a cause of bleeding from the upper urinary tract. This condition is characterized by infarction of the renal medullary vessels, leading to sloughing of the renal papillae and **gross hematuria**. RPN is common with sickle cell nephropathy or can occur with analgesic use, obstructive uropathy, or diabetes mellitus. Bleeding is often painless and self-limited.

(Choices A and E) Hematuria originating in the bladder (ie, lower urinary tract) can be due to rupture or malignancy. However, bladder wall rupture would appear as an open perforation (not two slit-like openings) and bladder cancer presents with a mass on cystoscopy.

(Choice B) A colovesical fistula, which most commonly causes air bubbles and stool within the urine, is typically seen as an erythematous and edematous opening in the bladder wall. Although hematuria can occur with concomitant gastrointestinal bleeding, this patient's 2 slit-like openings within the triangular portion of the bladder are consistent with anatomic ureteric orifices.

(Choice D) Urethral diverticulum, another cause of lower urinary tract bleeding, is an outpouching of the urethra that would be visualized on cystoscopy prior to insertion into the bladder. In addition to postvoid dribbling and frequent urinary tract infections, hematuria can occur in this condition but would be present only in the urethra, not in the bladder or ureters.

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In the absence of other findings, **renal papillary necrosis** (RPN) should also be considered as a cause of bleeding from the upper urinary tract. This condition is characterized by infarction of the renal medullary vessels, leading to sloughing of the renal papillae and **gross hematuria**. RPN is common with sickle cell nephropathy or can occur with analgesic use, obstructive uropathy, or diabetes mellitus. Bleeding is often painless and self-limited.

(Choices A and E) Hematuria originating in the bladder (ie, lower urinary tract) can be due to rupture or malignancy. However, bladder wall rupture would appear as an open perforation (not two slit-like openings) and bladder cancer presents with a mass on cystoscopy.

(Choice B) A colovesical fistula, which most commonly causes air bubbles and stool within the urine, is typically seen as an erythematous and edematous opening in the bladder wall. Although hematuria can occur with concomitant gastrointestinal bleeding, this patient's 2 slit-like openings within the triangular portion of the bladder are consistent with anatomic ureteric orifices.

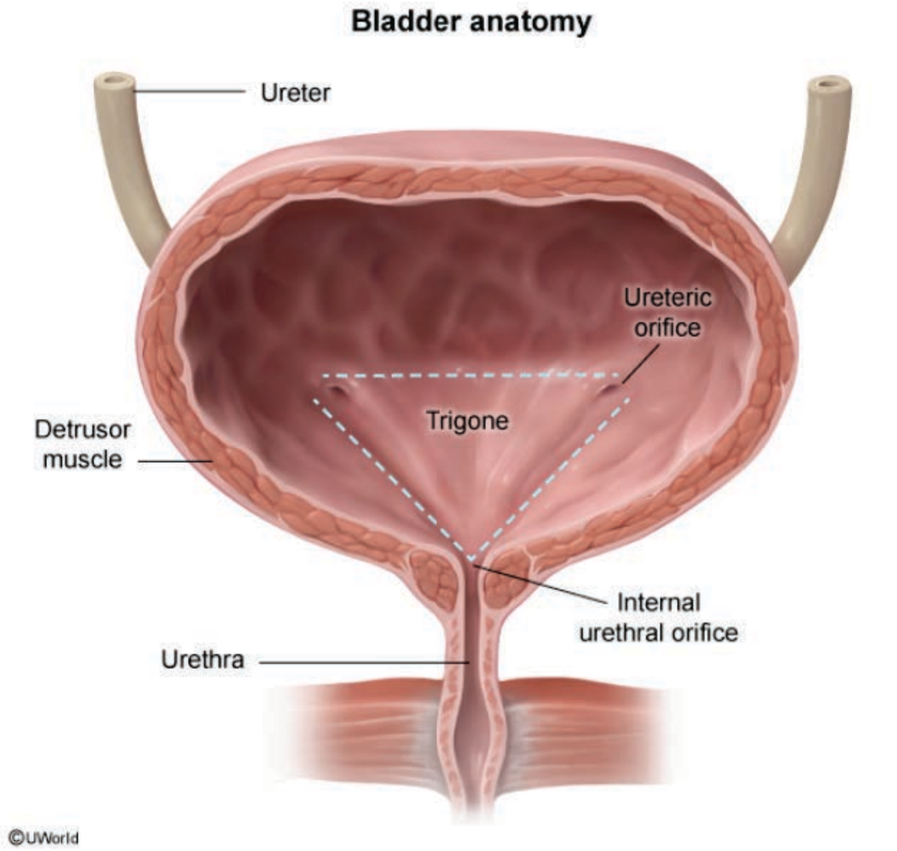
(Choice D) Urethral diverticulum, another cause of lower urinary tract bleeding, is an outpouching of the urethra that would be visualized on cystoscopy prior to insertion into the bladder. In addition to postvoid dribbling and frequent urinary tract infections, hematuria can occur in this condition but would be present only in the urethra, not in the bladder or ureters.

Educational objective:
The bladder trigone is formed by 2 slit-like ureteric orifices and the internal urethral opening. Blood within the ureteric orifice suggests upper urinary tract bleeding originating in the kidney (eg, renal papillary necrosis) or ureter.

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• Prostate cancer

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are consistent with anatomic ureteric orifices.

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A 34-year-old missionary in southern Asia is traveling to a remote village and becomes stranded when his bus breaks down. He has no access to water for 36 hours, during which his urine osmolality reaches 1100 mOsm/L. Urine concentration depends primarily on the serum level of vasopressin, which is regulated by the neurohypophysis in response to plasma osmolality and blood volume. Which of the following nephron segments responds to vasopressin by increasing absorption of a specific solute that is important for generating a high medullary concentration gradient?

- A. Cortical segment of the collecting duct
- B. Early distal tubule
- C. Medullary segment of the collecting duct
- D. Proximal tubule
- E. Thin ascending limb of the loop of Henle

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- A. Cortical segment of the collecting duct (22%)
- ✗ B. Early distal tubule (3%)
- ✓ C. Medullary segment of the collecting duct (60%)
- D. Proximal tubule (4%)
- E. Thin ascending limb of the loop of Henle (8%)

Incorrect
Correct answer
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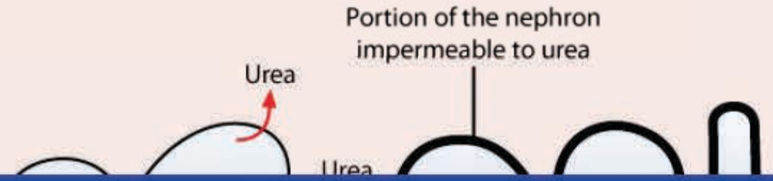
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Answered correctly

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Explanation

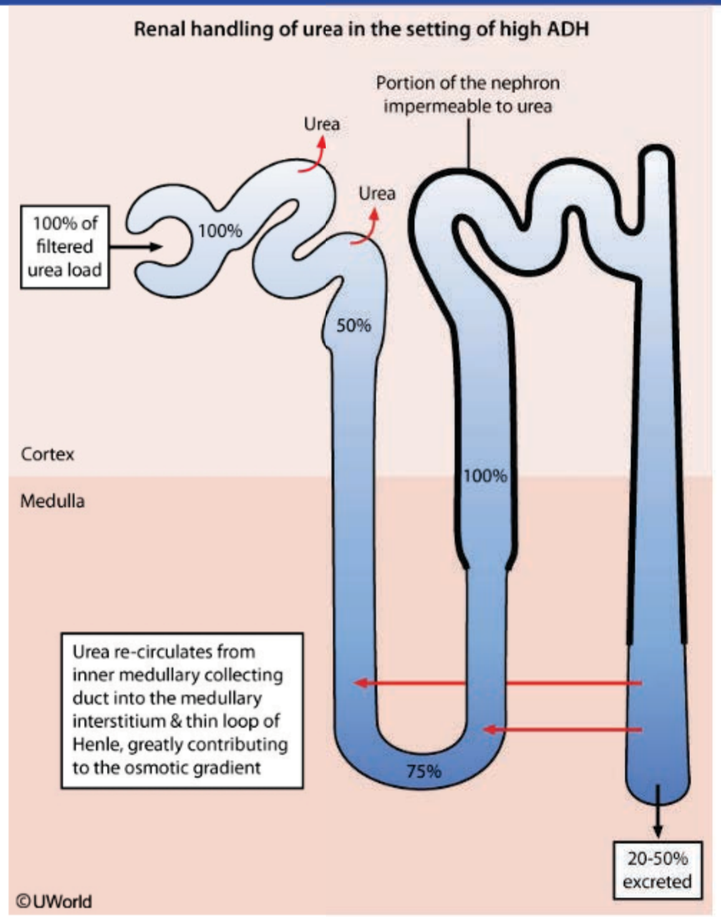
Renal handling of urea in the setting of high ADH



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Vasopressin, or antidiuretic hormone (ADH), is the primary physiologic inhibitor of free water excretion. This hormone acts on 2 major receptors, V1 and V2. Stimulation of the V1 receptor causes vasoconstriction and increased prostaglandin release; stimulation of the V2 receptor results in an antidiuretic response. ADH is secreted in response to plasma hyperosmolality and, to a lesser extent, depletion of the effective circulating volume. Water deprivation initially increases plasma osmolality, resulting in increased ADH secretion. This causes the kidney to produce concentrated urine, which helps to counteract the rise in plasma osmolality by reducing urinary free water excretion.

The medullary portion of the collecting duct is of particular importance in the production of maximally concentrated urine as the medullary interstitium is the region of highest osmolarity in the kidney. In the setting of high serum ADH levels, a large osmotic gradient drives the absorption of free water into the hypertonic medullary interstitium. As water leaves the tubular fluid, urea concentration greatly increases. ADH also increases the number of passive urea transporters in the inner medullary collecting duct, allowing a substantial fraction of the highly concentrated urea to diffuse down its concentration gradient into the medullary interstitium. When ADH levels are high, this urea resorption contributes up to 50% of total osmolarity of the medulla, further increasing the water-absorbing capacity of the nephron.

(Choice A) ADH also increases water absorption in the cortical segment of the collecting duct, reducing the amount of free water delivered to the medullary collecting duct. This prevents excess water from being absorbed into the medullary interstitium, which would otherwise dilute the osmotic gradient and reduce the maximum achievable urine concentration.

(Choice B) The early distal tubule is impermeable to both water and urea.

(Choice D) The proximal tubule is permeable to urea and resorbs about half of the filtered load. However, it does not respond to ADH.

(Choice E) The thin ascending limb of the loop of Henle is permeable to urea, which passively diffuses down its concentration gradient into the tubular lumen. Secretion of urea into the thin part of the loop of Henle allows urea

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urinary free water excretion.

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(Choice E) The thin ascending limb of the loop of Henle is permeable to urea, which passively diffuses down its concentration gradient into the tubular lumen. Secretion of urea into the thin part of the loop of Henle allows urea to recirculate and concentrate in the tubular system, further increasing its contribution to the medullary osmotic gradient.

Educational objective:
Antidiuretic hormone acts on the medullary segment of the collecting duct to increase urea and water reabsorption, allowing for the production of maximally concentrated urine.

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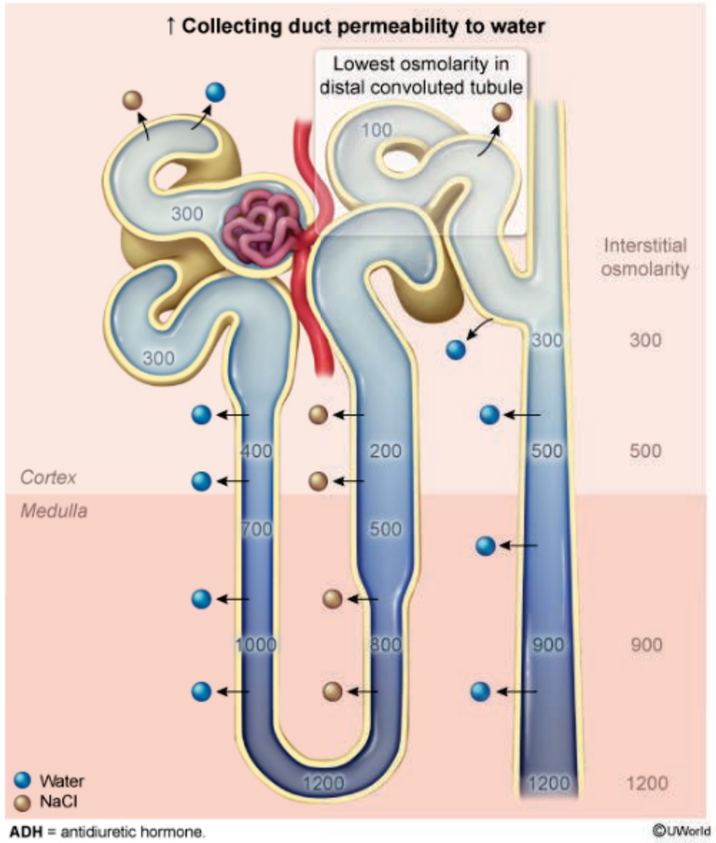
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Tubular fluid osmolarity in the setting of high ADH



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concentration gradient into the tubular lumen. Secretion of urea into the thin part of the loop of Henle allows urea

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A 38-year-old man is brought to the emergency department due to vomiting blood. After appropriate resuscitation measures, he undergoes upper gastrointestinal endoscopy, which reveals a bleeding duodenal ulcer. During hospital day 2, the patient develops decreased urine output. Serum creatinine rises to 3.0 mg/dL from a baseline of 1.2 mg/dL. Renal biopsy shows patchy epithelial necrosis of the tubules, tubulorrhexis, and intratubular casts. Supportive care is provided. Several days later, his urine output significantly increases and serum creatinine levels decline. Over the next few days, this patient is at highest risk for which of the following complications?

- A. Hyperphosphatemia
- B. Hypokalemia
- C. Metabolic acidosis
- D. Urinary protein loss
- E. Volume overload

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- A. Hyperphosphatemia (6%)
- ✓ B. Hypokalemia (61%)
- C. Metabolic acidosis (15%)
- D. Urinary protein loss (11%)
- E. Volume overload (5%)

Correct

61% Answered correctly

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Explanation

Stages of acute tubular necrosis	
Initiation stage (24-36 hours)	• Tubular injury resulting from: ◦ Ischemia (eg, hemorrhage, sepsis) ◦ Cytotoxins (eg, aminoglycosides, myoglobin)

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Explanation

Stages of acute tubular necrosis	
Initiation stage (24-36 hours)	• Tubular injury resulting from: ◦ Ischemia (eg, hemorrhage, sepsis) ◦ Cytotoxins (eg, aminoglycosides, myoglobin)
Maintenance stage (days to weeks)	• Oliguric renal failure (↓ GFR, ↓ urine output, volume overload) • ↑ Creatinine & BUN, ↑ serum K & PO_4, metabolic acidosis
Recovery stage (weeks to months)	• Gradual increase in urine output, high-volume diuresis • Impairment of tubular resorptive function (electrolyte wasting)
BUN = blood urea nitrogen; **GFR** = glomerular filtration rate; **K** = potassium; **PO_4** = phosphate.	

This patient developed acute renal failure following gastrointestinal hemorrhage; renal biopsy showing tubular epithelial necrosis, tubulorrhexis (ie, cell rupture with loss of the basement membrane), and intratubular casts is consistent with **acute tubular necrosis** (ATN). ATN is characterized by tubular injury due to renal ischemia (eg, shock) or direct cytotoxicity (eg, radiologic contrast agents, aminoglycosides).

The clinical course of ATN takes place in 3 stages. The **initiation** stage is marked by the inciting event (eg, hemorrhage, as in this patient) and the onset of tubular injury. If significant tubular damage occurs, the **maintenance** stage (oliguric stage) follows in 24-36 hours. During this stage, **urine output decreases** and

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Despite the seemingly profound damage that occurs to nephrons in ATN, tubular epithelial cells have excellent regenerative capacity. If the patient survives the maintenance stage (via conservative management or dialysis), the **recovery** stage follows in several days or up to several weeks. Glomerular filtration rate often improves before renal tubular resorptive function is restored, so patients can develop **transient polyuria** (sometimes >3 L/day) with significant **electrolyte wasting**. During this time, patients are at high risk for developing clinically significant electrolyte imbalances, particularly **hypokalemia**, which can be life threatening. Low serum concentrations of magnesium, phosphorus, and calcium may also develop. Depending on the magnitude of the initial injury, most patients eventually recover both glomerular filtration and tubular resorptive function.

(Choices A, C, and E) Hyperphosphatemia, anion gap metabolic acidosis, and volume overload occur in the maintenance stage of ATN. This patient's spontaneous diuresis and falling creatinine are more consistent with the recovery phase.

(Choice D) Protein-losing nephropathies (eg, nephrotic syndrome) occur due to significant glomerular damage. Because the destruction in ATN is largely tubular, protein loss is unexpected. Patients with nephrotic syndrome typically develop progressive renal dysfunction, which is not expected to improve after several days.

Educational objective:

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Educational objective:
Acute tubular necrosis is characterized by tubular injury due to renal ischemia or direct cytotoxicity. The course of the disease takes place in 3 stages: initiation (initial insult), maintenance (oliguric renal failure), and recovery. During the recovery stage, glomerular filtration rate improves prior to restoration of renal tubular resorptive capacity, so transient polyuria and electrolyte wasting (eg, hypokalemia) can occur.

References

- Acute renal tubular necrosis

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A 55-year-old woman comes to the office due to swelling around her ankles and face that has progressively worsened over the last 1-2 months. The patient has 2+ bilateral pitting edema in the lower extremities, trace edema in the upper extremities, and periorbital edema. Cardiopulmonary examination is normal. Laboratory evaluation shows a serum creatinine level of 2.0 mg/dL and an albumin level of 2.8 g/dL. Urinalysis shows 3+ proteinuria and no hematuria or casts. A kidney biopsy is performed; light microscopic findings following staining with hematoxylin and eosin are shown in the image below:

Which of the following is the most likely explanation for this patient's biopsy findings?

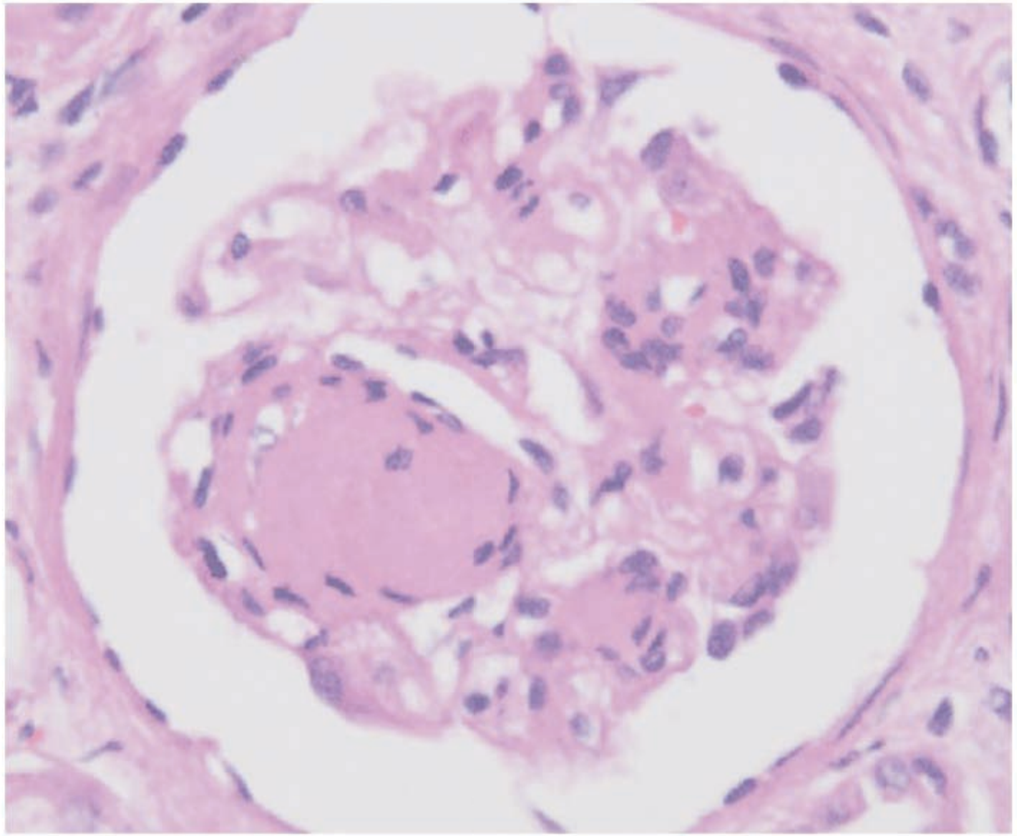
- A. Bee sting with severe allergic reaction
- B. Diabetes mellitus
- C. Hepatitis C infection
- D. HIV infection
- E. Lung carcinoma
- F. Recent streptococcal pharyngitis
- G. Systemic lupus erythematosus
- H. Treatment with procainamide

Submit

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A 55-year-old woman comes to the office due to swelling around her ankles and face that has progressively worsened over the past month. She has a history of hypertension and diabetes mellitus. Physical examination reveals edema of the lower extremities and periorbital edema. Laboratory evaluation reveals proteinuria and hypoalbuminemia. Renal biopsy is performed and a representative image is shown with

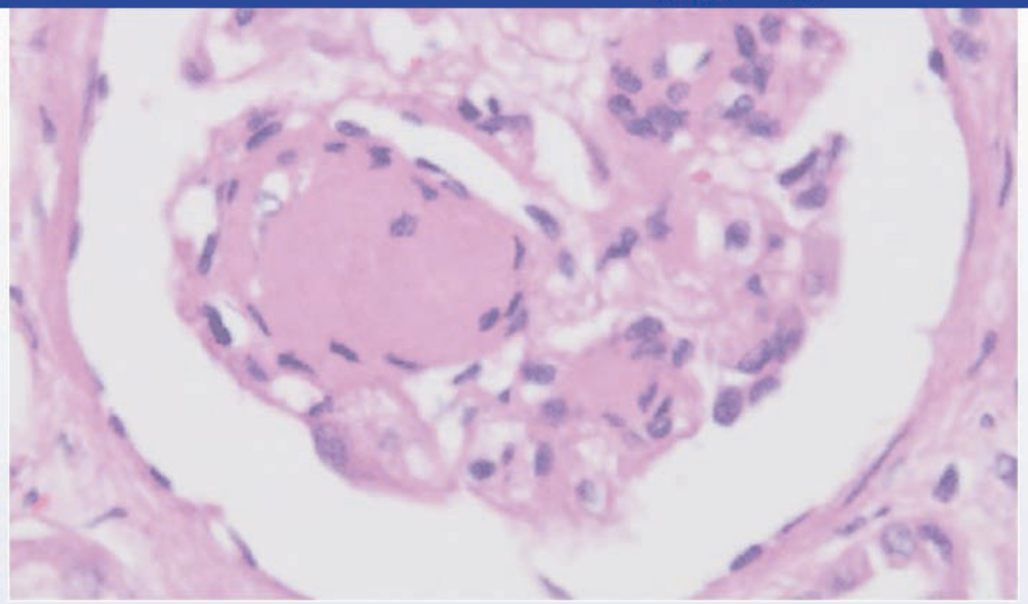
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Which of the following is the most likely explanation for this patient's biopsy findings?

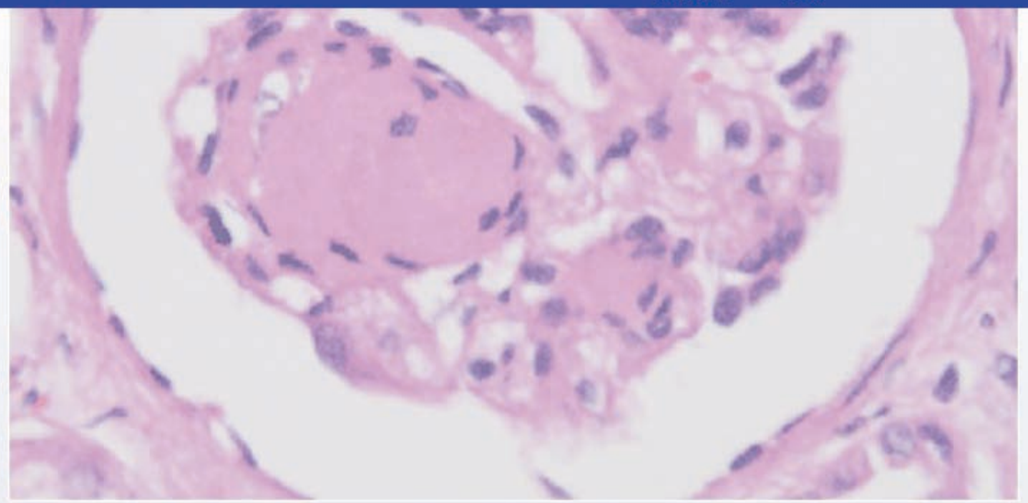
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Which of the following is the most likely explanation for this patient's biopsy findings?

- A. Bee sting with severe allergic reaction
- B. Diabetes mellitus
- C. Hepatitis C infection
- D. HIV infection
- E. Lung carcinoma
- F. Recent streptococcal pharyngitis
- G. Systemic lupus erythematosus
- H. Treatment with procainamide

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Which of the following is the most likely explanation for this patient's biopsy findings?

- A. Bee sting with severe allergic reaction (1%)
- ✓ B. Diabetes mellitus (64%)
- C. Hepatitis C infection (6%)
- D. HIV infection (10%)
- E. Lung carcinoma (0%)
- F. Recent streptococcal pharyngitis (3%)
- ✗ G. Systemic lupus erythematosus (10%)
- H. Treatment with procainamide (1%)

Incorrect
Correct answer
B

64%
Answered correctly

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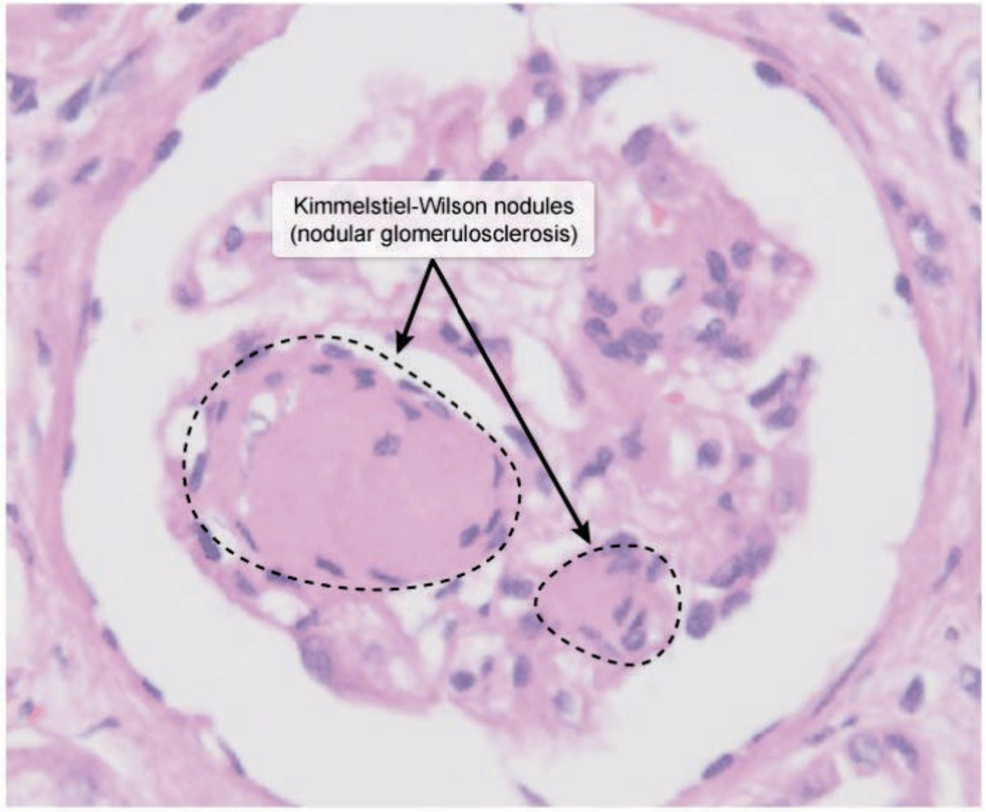
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Explanation

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Diabetic nephropathy



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- location in the peripheral mesangium

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This patient's renal biopsy shows Kimmelstiel-Wilson (KW) nodules, characterized by:

- location in the peripheral mesangium
- ovoid or spherical shape
- lamellated appearance
- eosinophilic appearance (hematoxylin and eosin stain)
- periodic acid–Schiff positivity

KW nodules are diagnostic for **nodular glomerulosclerosis**, characterized by **increased mesangial matrix deposition**. Over time, mesangium expansion and KW nodule formation compress the glomerular capillaries, causing loss of glomerular function. Progressive proteinuria can lead to overt **nephrotic syndrome** (eg, peripheral edema, heavy proteinuria, fatty casts), hypertension, and **renal failure**. The urine sediment is typically bland (ie, no dysmorphic red cells or red cell casts).

Nodular glomerulosclerosis, most commonly caused by diabetic nephropathy (type 1 or 2 diabetes mellitus), indicates irreversible glomerular damage and predicts a rapid decline in kidney function. Additional features of diabetic nephropathy include glomerular basement membrane (GBM) thickening and hyaline arteriolosclerosis.

Other causes of nephrotic syndrome include the following:

(Choice A) Minimal change disease can occur as an immunologic reaction to pollen/dust, insect stings, infection, or immunization. Glomeruli appear normal on light microscopy (LM). Electron microscopy (EM) shows effacement of podocyte foot processes.

(Choice C) Membranoproliferative glomerulonephritis is often associated with hepatitis B or C. LM shows hypercellular glomeruli with thickening and splitting of the GBM due to subendothelial immune complex (IC) deposition.

(Choice D) Focal segmental glomerulosclerosis can be associated with HIV infection, heroin use, and severe obesity. LM shows sclerotic changes in some portions of some glomeruli (eg, consolidation of a portion of a

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or immunization. Glomeruli appear normal on light microscopy (LM). Electron microscopy (EM) shows effacement of podocyte foot processes.

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(Choice D) Focal segmental glomerulosclerosis can be associated with HIV infection, heroin use, and severe obesity. LM shows sclerotic changes in some portions of some glomeruli (eg, consolidation of a portion of a glomerulus with capillary loops replaced by collagenous scar).

(Choice E) Solid tumors (eg, lung, breast, prostate) are associated with membranous nephropathy. LM shows capillary wall thickening and "membrane spikes" between subepithelial deposits on silver staining.

In contrast, a predominantly nephritic presentation (eg, hematuria, red cell casts, variable proteinuria) may be caused by the following:

(Choice F) In poststreptococcal glomerulonephritis, LM shows diffuse glomerular hypercellularity due to leukocyte infiltration and mesangial cell proliferation. Immunofluorescence shows IgG and C3 deposits, which can be visualized on EM as subepithelial humps.

(Choices G and H) Lupus nephritis most frequently manifests as diffuse proliferative glomerulonephritis. Drug-induced lupus (eg, procainamide, hydralazine, isoniazid) can rarely cause similar kidney involvement. LM frequently shows a variable pattern of mesangial proliferation and endocapillary hypercellularity. Wire loops (ie, thickened capillary walls due to subendothelial IC deposition) may also be seen.

Educational objective:
Nodular glomerulosclerosis is characterized by increased mesangial matrix deposition, forming Kimmelstiel-Wilson nodules. It is most commonly caused by diabetic nephropathy and indicates irreversible glomerular damage with a rapid decline in kidney function.

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- ovoid or spherical shape
- lamellated appearance
- eosinophil
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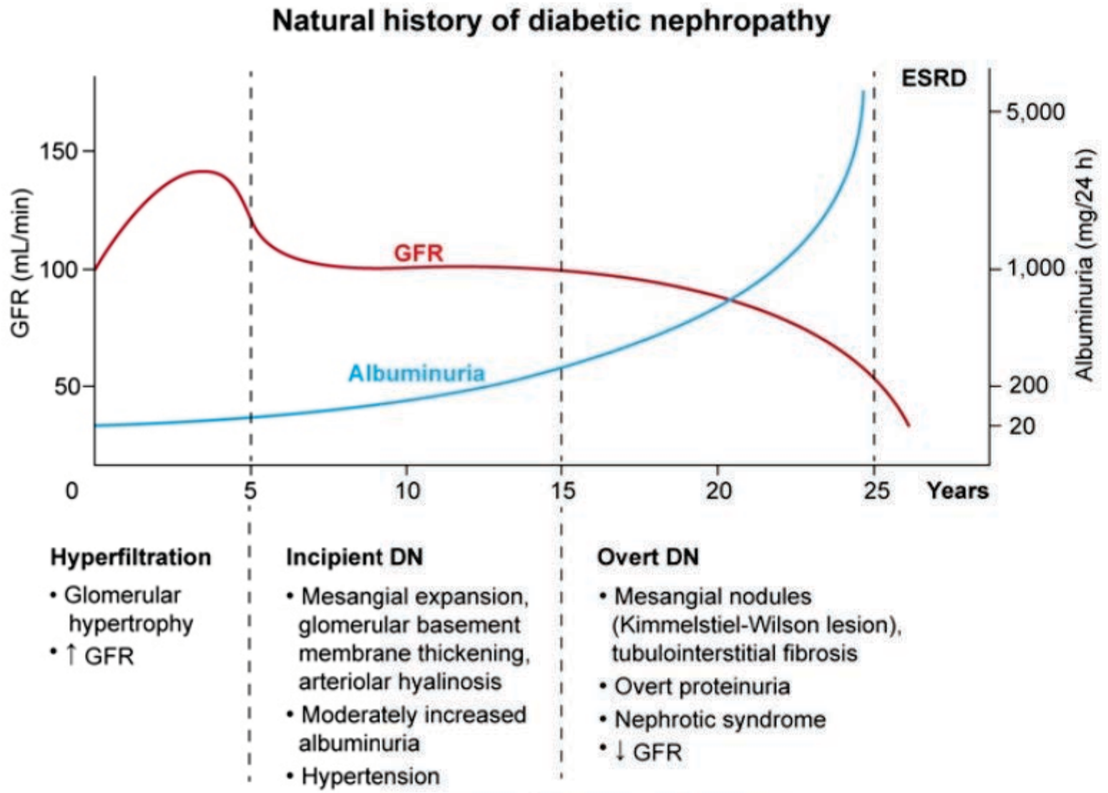
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(Choice C) M
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DN = diabetic nephropathy; **ESRD** = end-stage renal disease; **GFR** = glomerular filtration rate.
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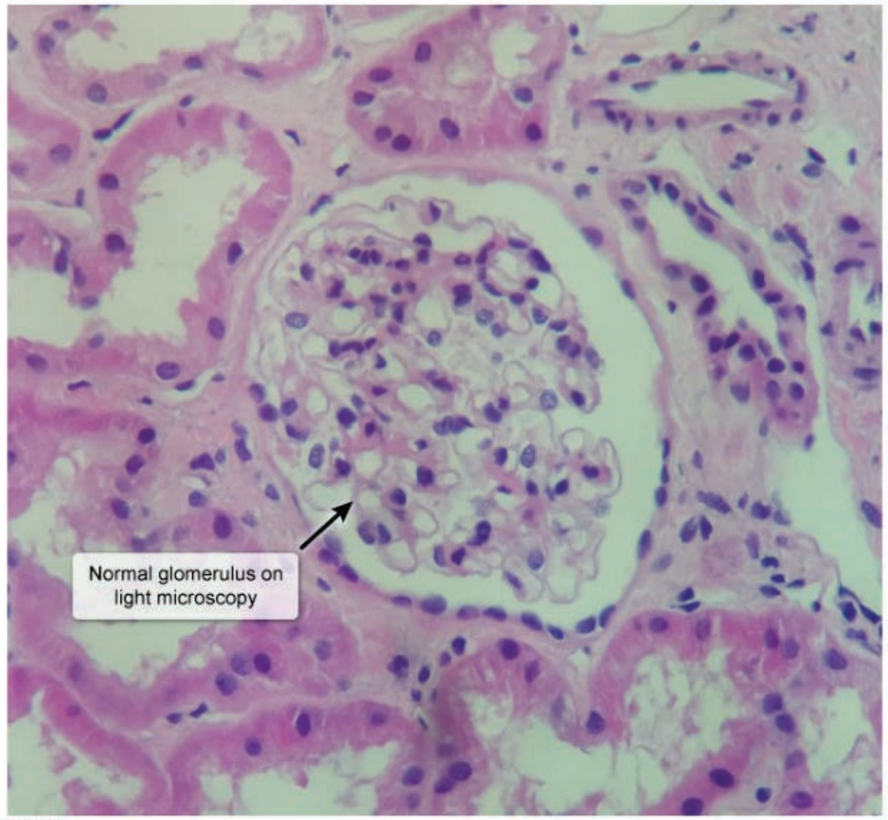
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Minimal change disease



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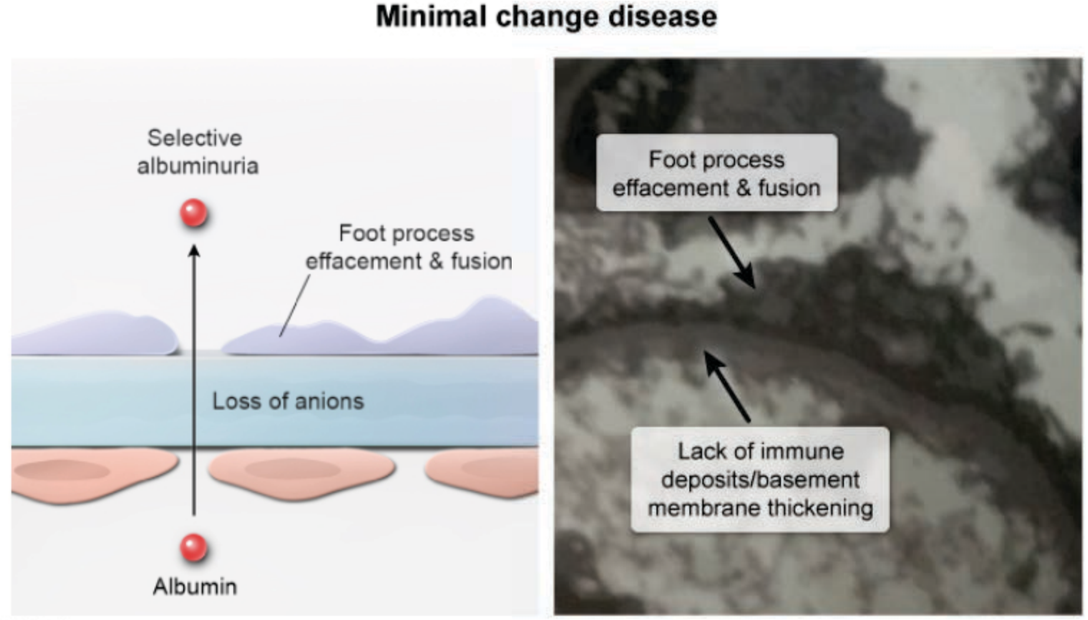
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(Choice E) Solid tumors (eg, lung, breast, prostate) are associated with membranous nephropathy. LM shows

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- periodic acid–Schiff positivity

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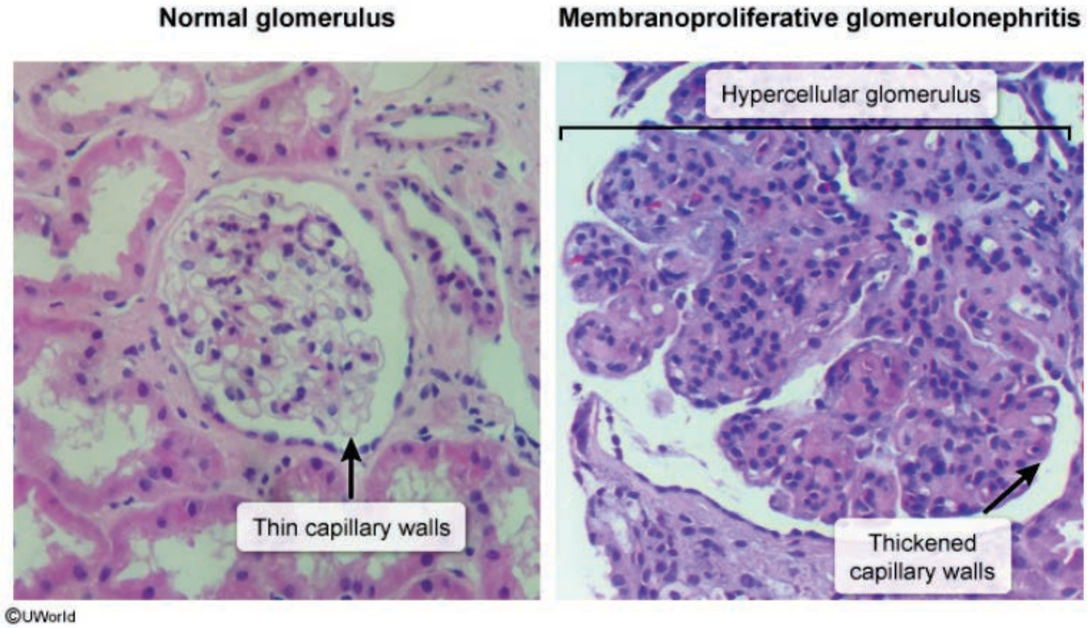
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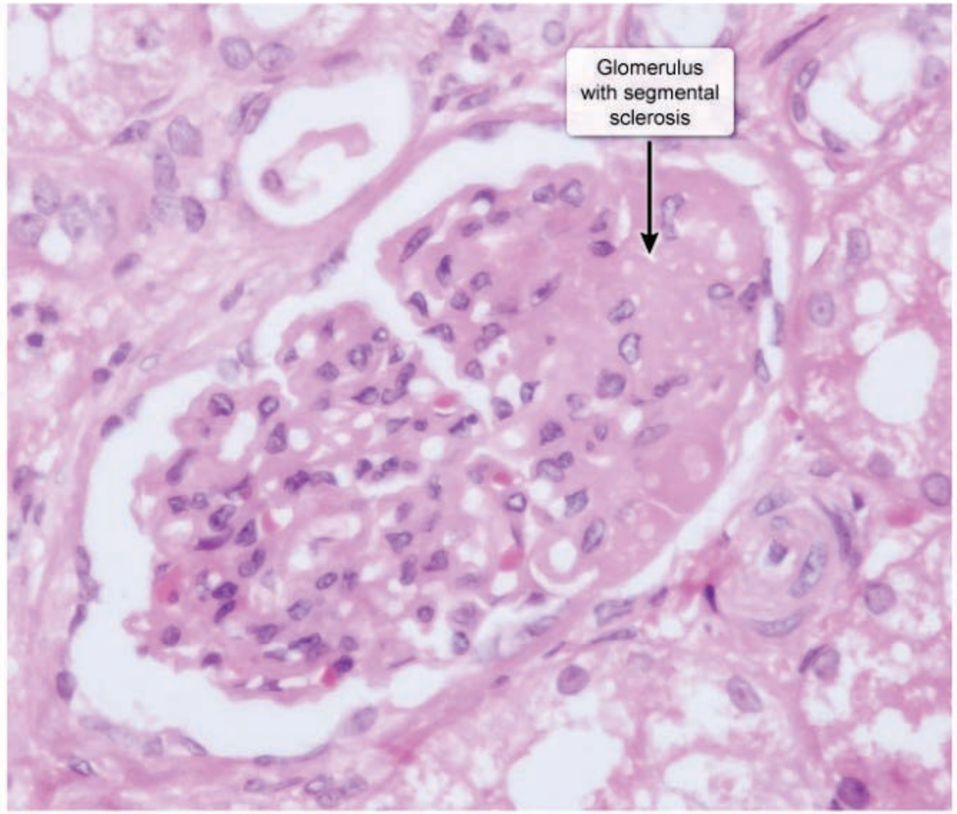
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Focal segmental glomerulosclerosis



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diabetic nephropathy include glomerular basement membrane (GBM) thickening and hyaline arteriolosclerosis.

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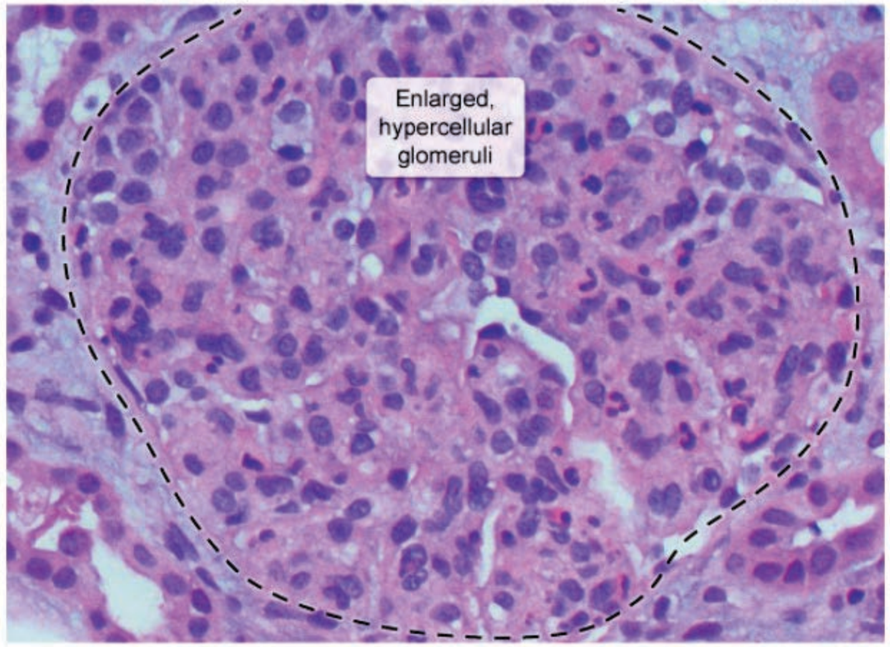
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Educational objective:

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Acute postinfectious glomerulonephritis



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A clinical trial of a novel drug X is being conducted. Animal studies have shown that the drug is eliminated primarily by the kidneys. A healthy volunteer of body weight 60 kg (132.3 lb) is recruited, and his glomerular filtration rate is 100 mL/min. In this volunteer, plasma concentration of the drug, immediately after intravenous administration, is 0.5 mg/mL. Urinary excretion rate of the drug is found to be 75 mg/min. When another medication, drug Y, is coadministered, urinary excretion rate of the drug X is 50 mg/min. Which of the following effects of drug Y on the pharmacokinetics of drug X best explains the findings in this study?

- A. Decreased renal tubular reabsorption
- B. Decreased renal tubular secretion
- C. Displacement from plasma proteins
- D. Increased glomerular filtration

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- A. Decreased renal tubular reabsorption (4%)
- ✓ B. Decreased renal tubular secretion (88%)
- C. Displacement from plasma proteins (5%)
- D. Increased glomerular filtration (2%)

Correct

88%
Answered correctly

15 mins, 37 secs
Time Spent

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Explanation

Renal excretion is a major mechanism of drug removal. This process is dependent on **glomerular filtration**, **tubular secretion,** and **tubular reabsorption** of the drug. Therefore, factors that reduce renal drug excretion and lead to increased plasma drug levels include the following:

- **Reduced glomerular filtration:** Kidney disease (eg, chronic kidney disease from diabetes mellitus) and reduced renal blood flow (eg, NSAID-induced vasoconstriction, volume contraction) lead to reduced drug filtration. In addition, plasma proteins are not filtered at the glomerulus; therefore, highly protein-bound drugs are not effectively filtered

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- **Reduced glomerular filtration:** Kidney disease (eg, chronic kidney disease from diabetes mellitus) and reduced renal blood flow (eg, NSAID-induced vasoconstriction, volume contraction) lead to reduced drug filtration. In addition, plasma proteins are not filtered at the glomerulus; therefore, highly protein-bound drugs are not effectively filtered.
- **Reduced renal tubular secretion:** Active transport of drugs is largely dependent on transporters (eg, organic anion or cation transporter). Coadministration of drugs with overlapping substrate specificity can result in competition for or inhibition of transporters.
- **Increased renal tubular reabsorption:** Only polarized (ionized) drugs are water soluble, whereas nonionized forms are lipid soluble and can passively diffuse across the renal tubular membrane to reenter the plasma. Therefore, alterations in urine pH can augment drug excretion; for example, acidification of urine favors the reabsorption of acidic drugs because a greater proportion of the drug is in the nonionized form.

The urinary excretion rate of drug X was reduced from 75 to 50 mg/min after the administration of drug Y. Of the options available, only **decreasing the renal tubular secretion** of drug X reduces its excretion rate. Drug Y likely had similar specificity for active transporters in the renal tubules, limiting or inhibiting the secretion of drug X.

(Choices A, C, and D) Decreased renal tubular reabsorption, displacement from plasma proteins, and increased glomerular filtration would all increase the excretion rate of drug X.

Educational objective:
Renal excretion of a drug is dependent on:

- Glomerular filtration (reduced with low renal blood flow, kidney disease, and high drug protein binding)
- Renal tubular secretion (reduced by coadministration of drugs with overlapping substrate specificity)

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lead to increased plasma drug levels include the following:

- **Reduced glomerular filtration:** Kidney disease (eg, chronic kidney disease from diabetes mellitus) and reduced renal blood flow (eg, NSAID-induced vasoconstriction, volume contraction) lead to reduced drug filtration. In addition, plasma proteins are not filtered at the glomerulus; therefore, highly protein-bound drugs are not effectively filtered.
- **Reduced renal tubular secretion:** Active transport of drugs is largely dependent on transporters (eg, organic anion or cation transporter). Coadministration of drugs with overlapping substrate specificity can result in competition for or inhibition of transporters.
- **Increased renal tubular reabsorption:** Only polarized (ionized) drugs are water soluble, whereas nonionized forms are lipid soluble and can passively diffuse across the renal tubular membrane to reenter the plasma. Therefore, alterations in urine pH can augment drug excretion; for example, acidification of urine favors the reabsorption of acidic drugs because a greater proportion of the drug is in the nonionized form.

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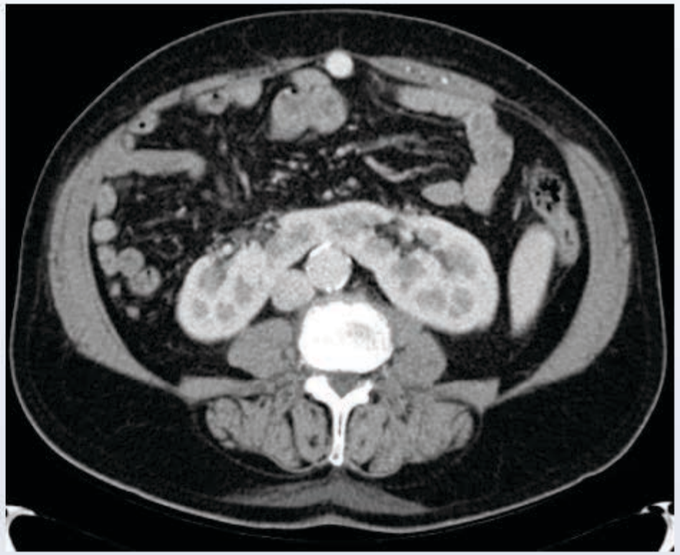
(Choices A, C, and D) Decreased renal tubular reabsorption, displacement from plasma proteins, and increased glomerular filtration would all increase the excretion rate of drug X.

Educational objective:
Renal excretion of a drug is dependent on:

- Glomerular filtration (reduced with low renal blood flow, kidney disease, and high drug protein binding)
- Renal tubular secretion (reduced by coadministration of drugs with overlapping substrate specificity)
- Tubular reabsorption (may be altered by changes in urine pH)

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A 47-year-old woman comes to the office due to fever, dysuria, and abdominal pain. The patient has had several urinary tract infections since her teens but has no other medical concerns. Physical examination shows mild suprapubic discomfort. Urinalysis demonstrates pyuria and many bacteria. CT scan of the abdomen is shown in the image below:



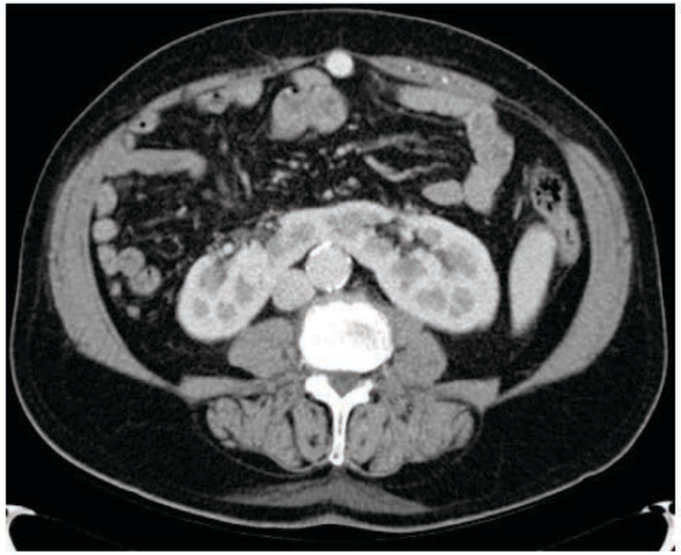
Which of the following structures has most likely limited the proper ascent of the anomalous organ seen on CT scan?

- A. Inferior mesenteric artery
- B. Inferior vena cava
- C. Persistent urachus
- D. Superior mesenteric artery
- E. Vitelline duct

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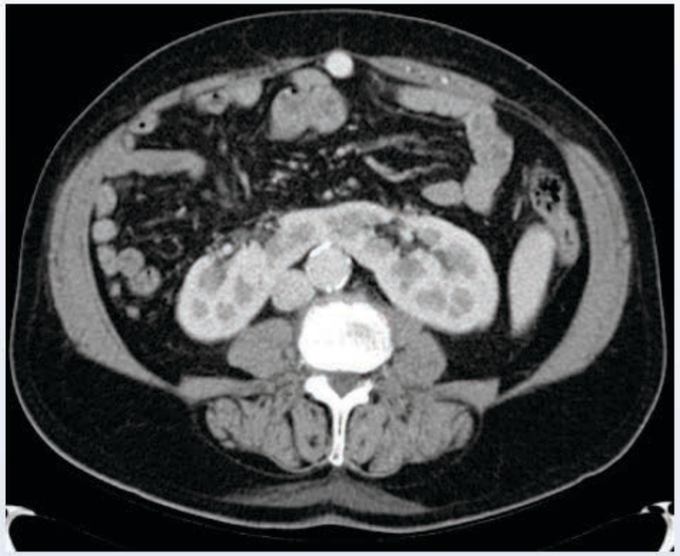
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suprapubic discomfort. Urinalysis demonstrates pyuria and many bacteria. CT scan of the abdomen is shown in the image below:



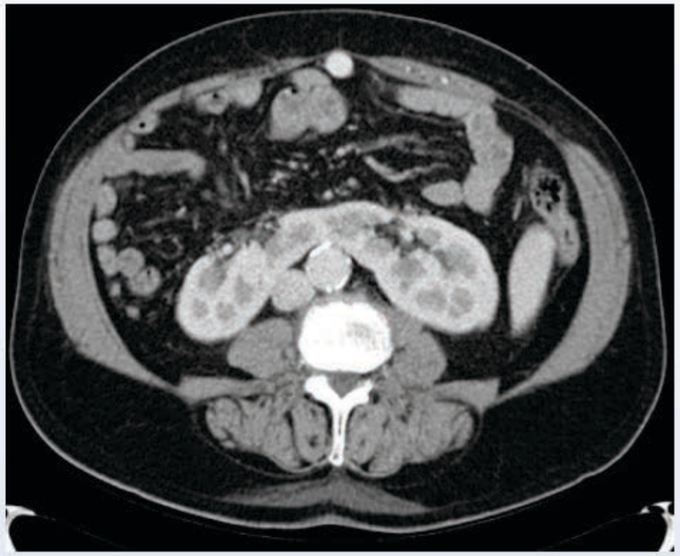
Which of the following structures has most likely limited the proper ascent of the anomalous organ seen on CT scan?

- A. Inferior mesenteric artery
- B. Inferior vena cava
- C. Persistent urachus
- D. Superior mesenteric artery
- E. Vitelline duct

Submit

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suprapubic discomfort. Urinalysis demonstrates pyuria and many bacteria. CT scan of the abdomen is shown in the image below:



Which of the following structures has most likely limited the proper ascent of the anomalous organ seen on CT scan?

- ✓ A. Inferior mesenteric artery (73%)
- B. Inferior vena cava (3%)
- ✗ C. Persistent urachus (6%)
- D. Superior mesenteric artery (12%)
- E. Vitelline duct (2%)

Incorrect
Correct answer
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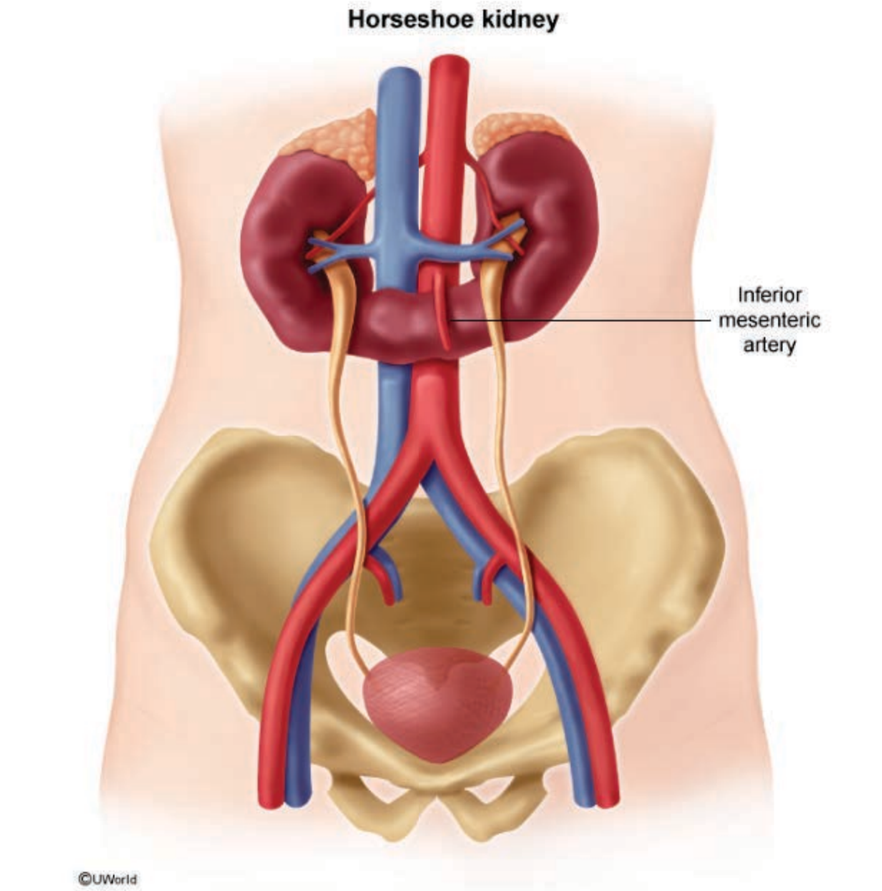
73%
Answered correctly

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This patient's CT scan of the abdomen reveals fusion of the kidneys at their lower poles, conjoining them into a horseshoe shape (ie, **horseshoe kidney**). This fusion can occur alone or can be associated with other genitourinary tract abnormalities and chromosomal aneuploidy (eg, trisomy 18, Turner syndrome).

During kidney development, the metanephric blastema (ie, embryonic kidney precursor) is initially located in the sacral region. The relative ascent of the kidneys to their normal anatomic position (T12-L3 in adults) results from the disproportionately rapid growth of the caudal portion of the fetus. As the horseshoe kidney ascends from the sacral region, the **central isthmus** (ie, fused portion) becomes caught on the **inferior mesenteric artery**, limiting further ascent.

Although typically asymptomatic, the anatomic abnormalities in patients with horseshoe kidney place them at increased risk for ureteropelvic junction obstruction, recurrent infection, and nephrolithiasis.

(Choice B) The inferior vena cava lies posterior to the isthmus of a horseshoe kidney and would not obstruct its ascent.

(Choices C and E) A direct connection between the bladder lumen and the outside of the body at the umbilicus is called a patent urachus or urachal fistula. When the connection is between the intestinal lumen and the outside of the body at the umbilicus, it is due to a persistent vitelline duct. These connections would likely have been identified earlier in the patient's life and would not affect the ascent of a horseshoe kidney.

(Choice D) The superior mesenteric artery is located above the inferior mesenteric artery. It leaves the aorta at the level of L1 and does not serve as an obstacle for the ascent of a horseshoe kidney.

Educational objective:
During embryologic development, fusion of the kidneys at their lower poles (horseshoe kidney) may prevent ascent of the kidneys from the pelvis. Although most patients remain asymptomatic, they are at increased risk for ureteropelvic junction obstruction, recurrent infection, and nephrolithiasis.

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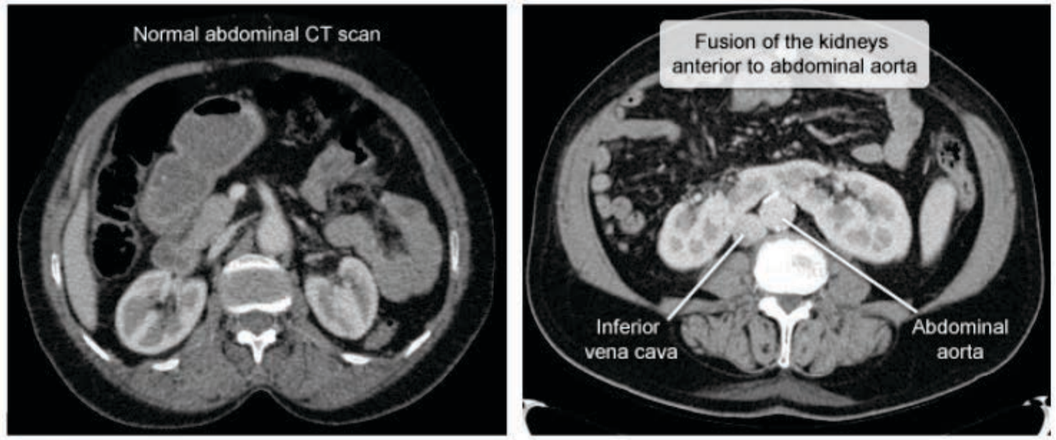
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Horseshoe kidney



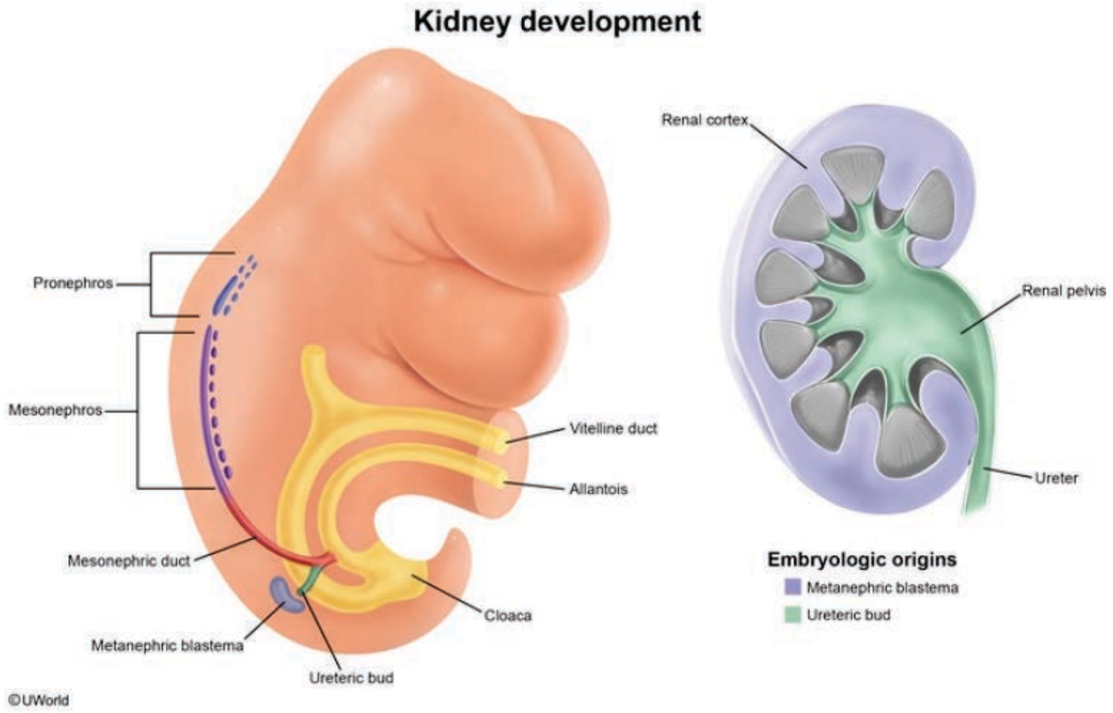
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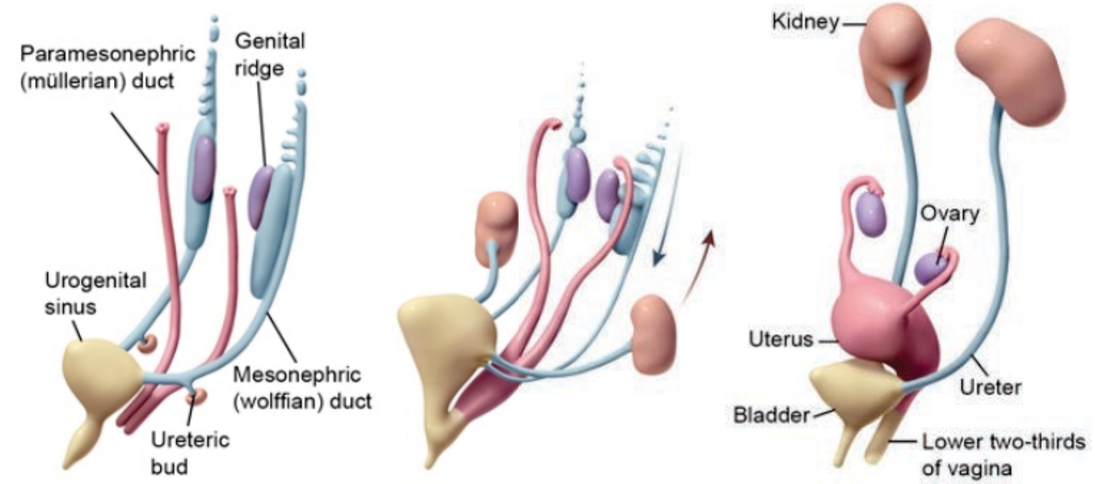
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Urogenital development



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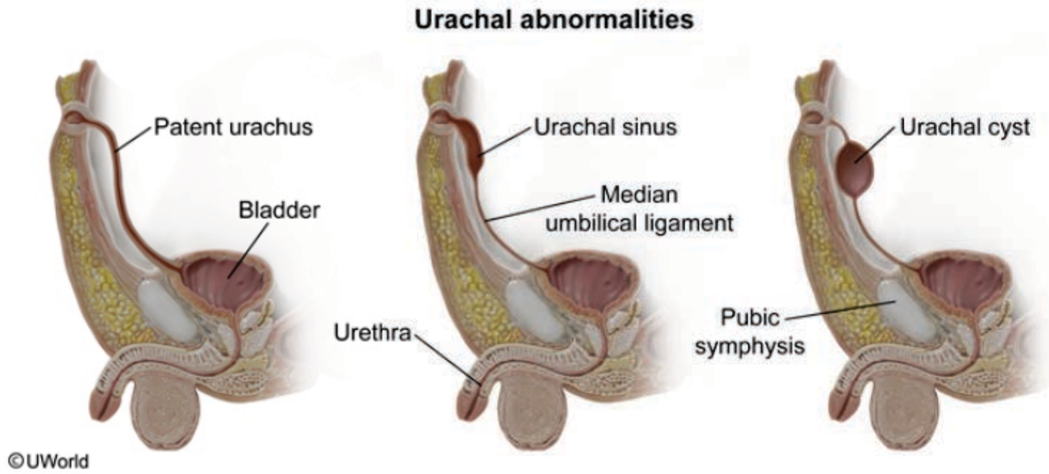
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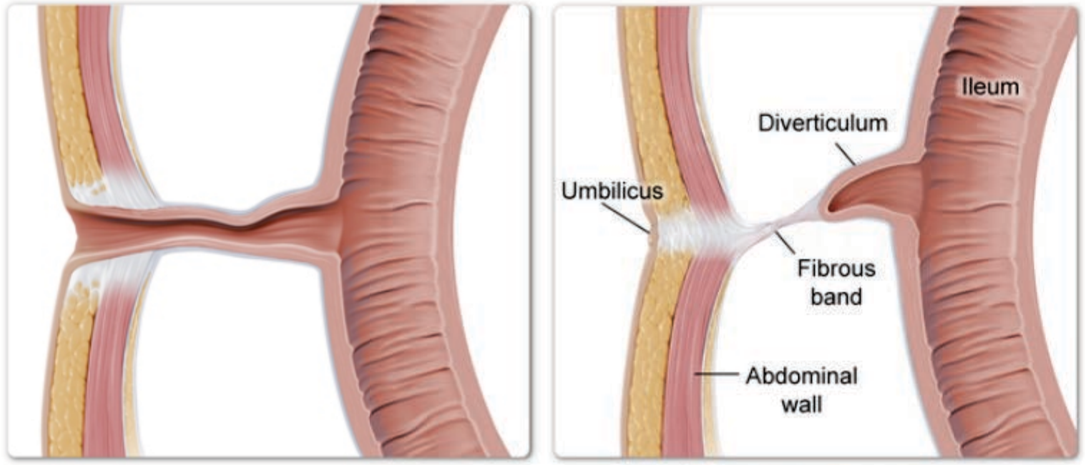
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Vitelline duct abnormalities



Persistent vitelline duct

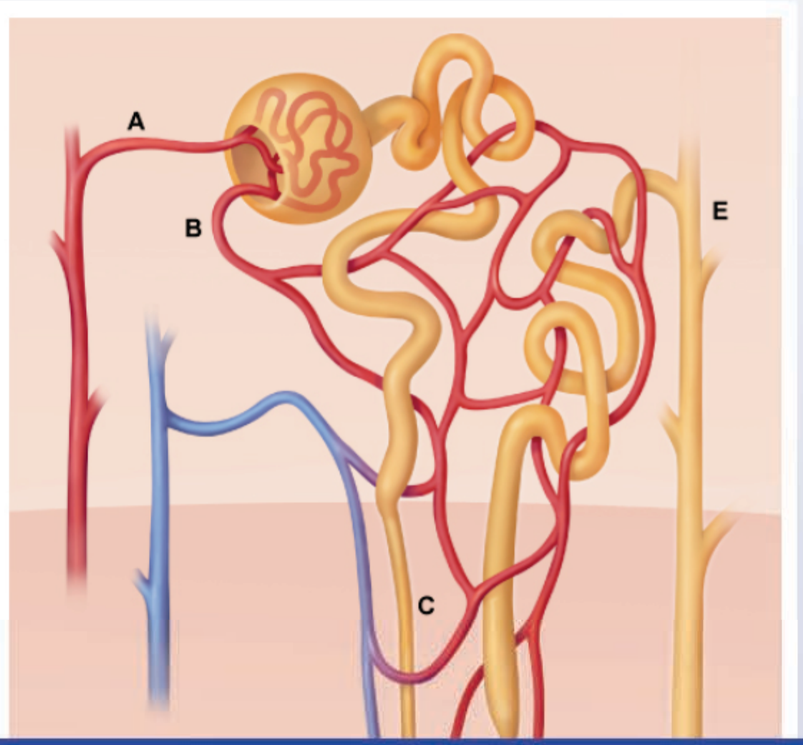
Meckel diverticulum (most common)

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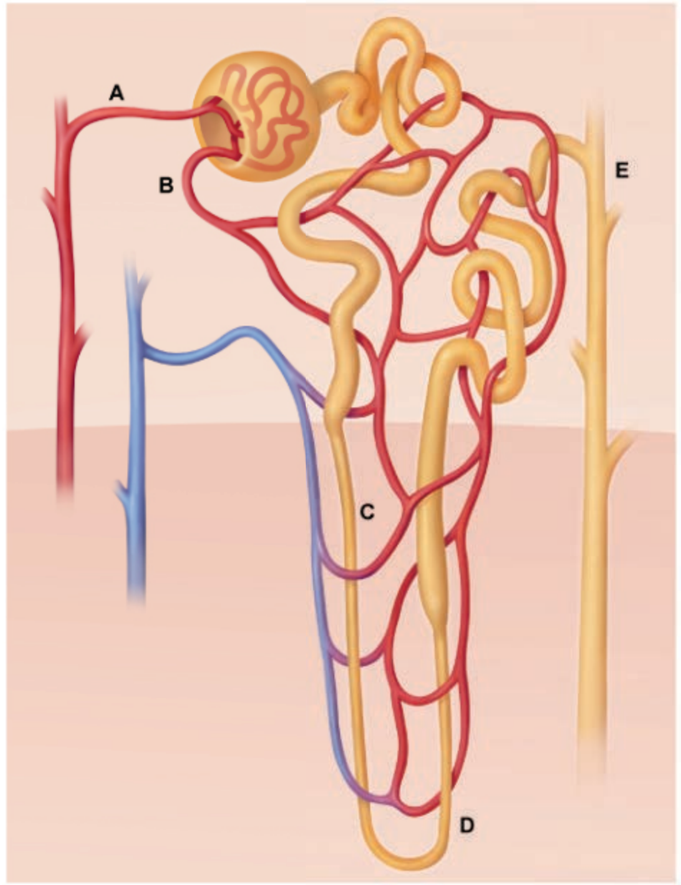
A 64-year-old man comes to the office after learning at the dentist's office that he has elevated blood pressure. The patient is a combat veteran and has always been "fit as a bull." He has undergone various minor surgical procedures for wartime injuries. He reports many years of tobacco and alcohol use but currently uses neither. On careful questioning, he describes chest pain on exertion. Blood pressure is 155/90 mm Hg and pulse is 76/min. Physical examination is significant for decreased pulse amplitude over the right femoral artery and a systolic bruit over the left carotid artery. Resting ECG is unremarkable, and serum creatinine is 1.1 mg/dL. Urinalysis is negative for protein. Treatment for hypertension is initiated with ramipril. On a follow-up visit 3 weeks later, blood pressure is 142/85 mm Hg but serum creatinine has increased to 2 mg/dL. This laboratory finding is best explained by an effect of the drug on which of the following structures (as indicated in the image)?



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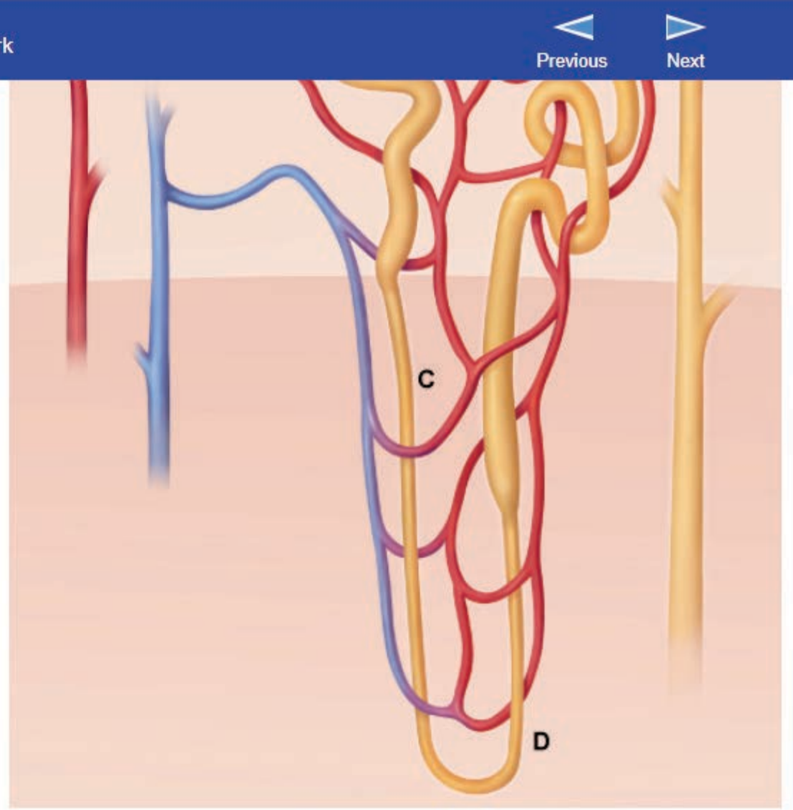
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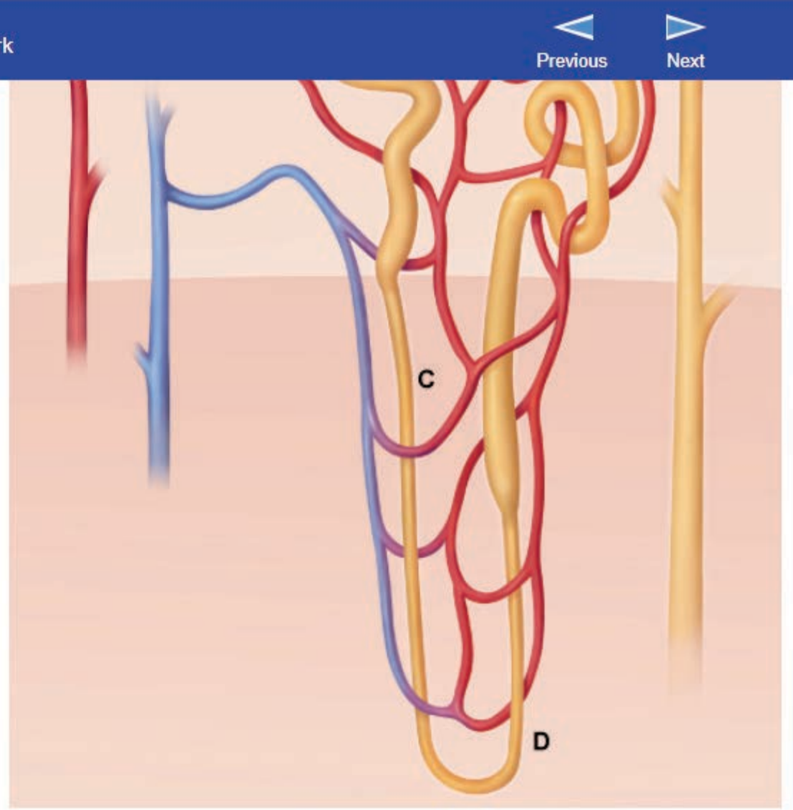
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- A. A
- B. B
- C. C
- D. D
- E. E

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- A. A (14%)
- ✓ B. B (77%)
- C. C (1%)
- ✗ D. D (1%)
- E. E (5%)

Incorrect
Correct answer
B

77%
Answered correctly

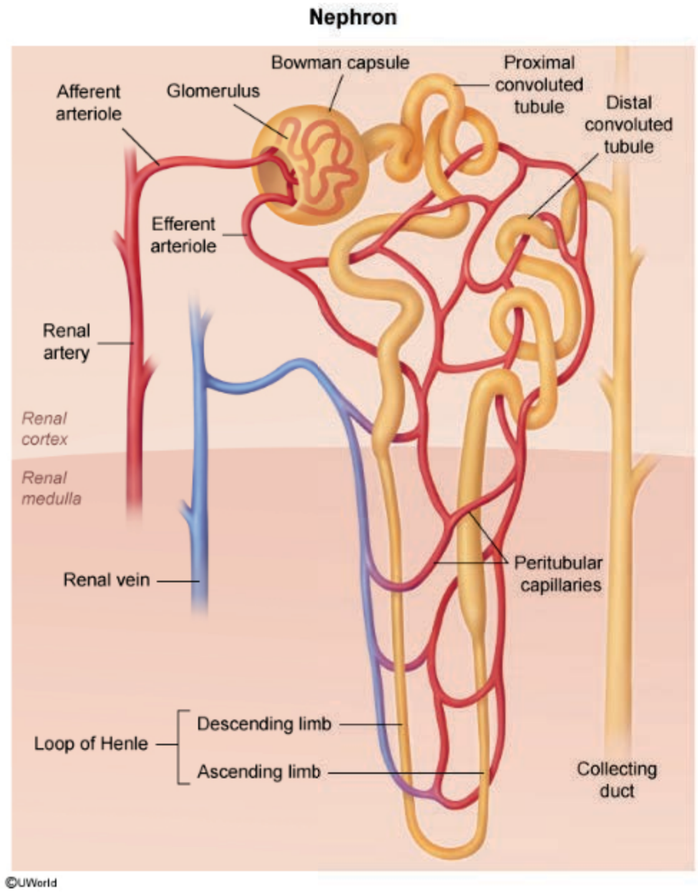
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Explanation

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Ascending limb
Collecting duct

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This patient with angina, reduced femoral pulsation, and a carotid bruit has diffuse atherosclerosis. Patients with severe atherosclerosis or atherosclerotic risk factors (eg, hypertension, hyperlipidemia, smoking) are more likely to develop atherosclerotic **renal artery stenosis** (RAS). Conditions that reduce renal perfusion (eg, hypovolemia, congestive heart failure, RAS [as in this patient]) lower glomerular filtration pressure and the glomerular filtration rate (GFR), stimulating the renin-angiotensin-aldosterone system. This results in increased levels of **angiotensin II**, a potent vasoconstrictor that causes systemic hypertension and preferentially **constricts the efferent arteriole** to restore GFR.

ACE inhibitors lower angiotensin II levels, causing systemic vasodilation and reduced blood pressure. However, they also cause **efferent arteriolar dilation** and lower intraglomerular pressure, preventing the kidney from maintaining GFR in the setting of reduced renal perfusion. Many patients experience up to a 30% increase in serum creatinine within 2-5 days of starting ACE inhibitors. Patients with bilateral RAS (who are heavily dependent on angiotensin II to maintain GFR) can experience a precipitous fall in GFR and develop **acute renal failure**.

(Choice A) Locally produced vasodilators (prostaglandins and nitric oxide) in the afferent arteriole counteract the vasoconstrictive effects of angiotensin II; as a result ACE inhibitors do not significantly affect the afferent arterioles. However, nonsteroidal anti-inflammatory drugs (eg, ibuprofen) and calcineurin inhibitors (eg, cyclosporine) inhibit prostaglandin formation, resulting in constriction of the afferent arterioles and a reduction in intraglomerular pressure.

(Choices C and D) Aminoglycosides, vancomycin, certain antiretrovirals (eg, cidofovir), and foscarnet can damage the renal tubular cells, resulting in acute tubular necrosis. However, ACE inhibitors are not directly toxic to the renal tubules and have no effect on the descending or ascending loop of Henle.

(Choice E) ACE inhibitors block the release of aldosterone, resulting in decreased Na^+ reabsorption and K^+ secretion in the distal and collecting tubules. Although this effect is responsible for the hyperkalemia often seen with ACE inhibitor therapy, it would not cause the rise in creatinine.

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(Choice E) ACE inhibitors block the release of aldosterone, resulting in decreased Na^+ reabsorption and K^+ secretion in the distal and collecting tubules. Although this effect is responsible for the hyperkalemia often seen with ACE inhibitor therapy, it would not cause the rise in creatinine.

Educational objective:
ACE inhibitors reduce angiotensin II levels and cause efferent arteriole dilation, thereby decreasing the glomerular filtration pressure and filtration rate. This can precipitate acute renal failure in patients with reduced intrarenal perfusion pressure at baseline (eg, renal artery stenosis, congestive heart failure, hypovolemia).

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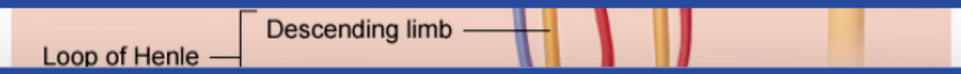
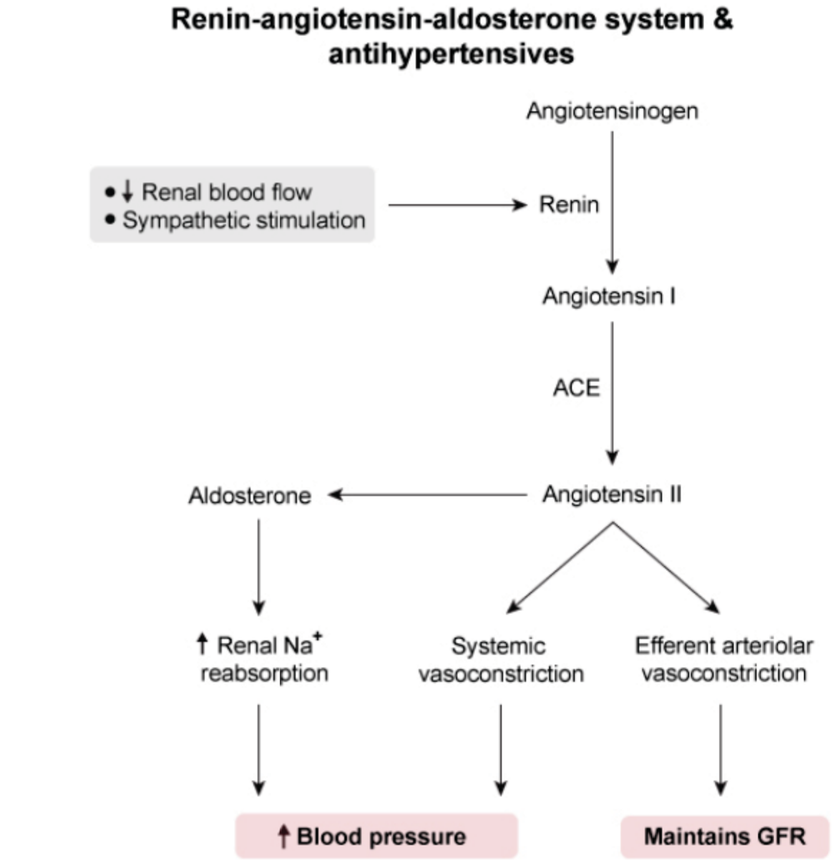


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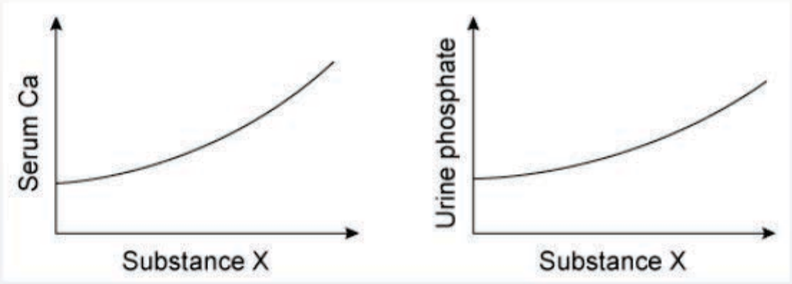
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A group of researchers is developing new drugs for osteoporosis. They are testing a new drug, Substance X, that exhibits the following metabolic effects when given via an infusion in varying doses (as shown in the graphs below).



Which of the following most closely resembles the metabolic effects of Substance X?

- A. 1,25-dihydroxyvitamin D analog
- B. Fibroblast growth factor 23 inhibitor
- C. Pyrophosphate analog
- D. Receptor activator of nuclear factor kappa-B ligand (RANK-L) inhibitor
- E. Recombinant parathyroid hormone

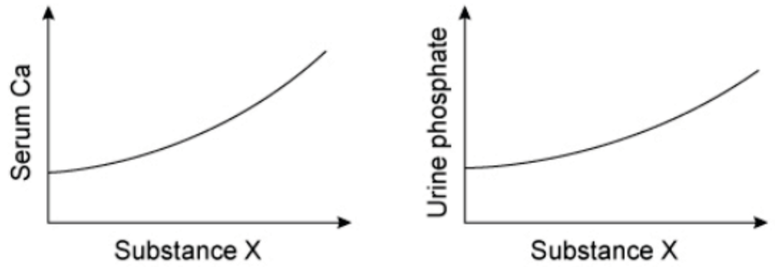
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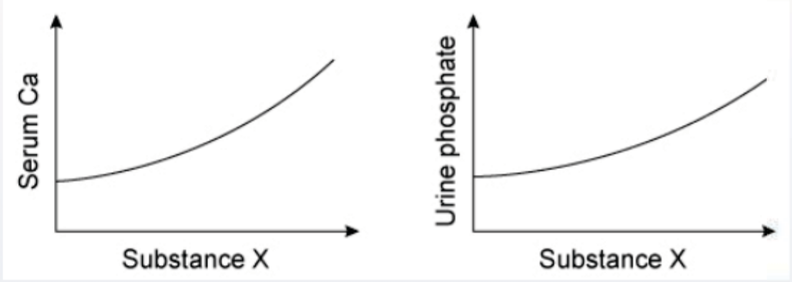
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A group of researchers is developing new drugs for osteoporosis. They are testing a new drug, Substance X, that exhibits the following metabolic effects when given via an infusion in varying doses (as shown in the graphs below).



Which of the following most closely resembles the metabolic effects of Substance X?

- A. 1,25-dihydroxyvitamin D analog (12%)
- ✗ B. Fibroblast growth factor 23 inhibitor (0%)
- C. Pyrophosphate analog (0%)
- D. Receptor activator of nuclear factor kappa-B ligand (RANK-L) inhibitor (1%)
- ✓ E. Recombinant parathyroid hormone (83%)

Incorrect
Correct answer
E

83%
Answered correctly

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Explanation

Parathyroid hormone, calcium, and phosphorus

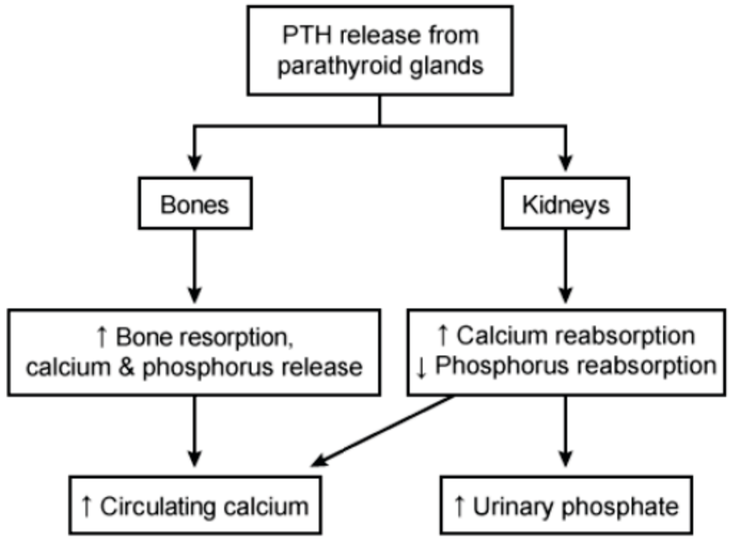
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Parathyroid hormone, calcium, and phosphorus



PTH = parathyroid hormone.

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PTH receptors are located on osteoblasts (not osteoclasts), and activation causes osteoblasts to increase production of receptor activator of nuclear factor kappa-B ligand (RANK-L) and monocyte colony-stimulating

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This investigational drug causes a dose-dependent increase in serum calcium and urine phosphate excretion, which resembles the activity of **parathyroid hormone** (PTH).

PTH receptors are located on osteoblasts (not osteoclasts), and activation causes osteoblasts to increase production of receptor activator of nuclear factor kappa-B ligand (RANK-L) and monocyte colony-stimulating factor. These factors stimulate osteoclastic precursors to differentiate into bone-resorbing osteoclasts. PTH also decreases the release of osteoprotegerin (OPG), a decoy receptor for RANK-L; therefore, lower levels of OPG allow for more interaction between RANK-L and the osteoclastic receptor, **increasing bone resorption** and **releasing calcium and phosphate** into circulation. In the kidney, PTH **decreases tubular reabsorption of phosphorus** while increasing reabsorption of calcium. Therefore, the combined effects are **increased serum calcium** and **urine phosphate levels**.

Chronically high levels of PTH (ie, hyperparathyroidism) increase the risk of osteoporosis. However, intermittent administration of recombinant PTH analogs induces a greater increase in osteoblast activity in proportion to osteoclast activity and a net increase in new bone formation. Teriparatide is a recombinant PTH analog used to treat osteoporosis.

(Choice A) PTH increases renal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, which increases intestinal absorption of calcium and phosphate and decreases PTH secretion via negative feedback. 1,25-dihydroxyvitamin D analogs (eg, calcipotriol) can raise serum calcium to some extent, but suppression of PTH limits the degree of phosphate excretion in the urine.

(Choice B) PTH increases renal phosphate excretion by inducing internalization and destruction of type IIa sodium/phosphate cotransporters (NPT2) in the proximal renal tubule. Fibroblast growth factor 23 (FGF23) is a hormone produced by osteocytes that acts synergistically with PTH to increase phosphate excretion by downregulating NPT2 gene expression. Investigational FGF23 inhibitors reduce renal phosphate excretion.

(Choices C and D) Bisphosphonates (eg, alendronate, risedronate) are pyrophosphate analogs that attach to hydroxyapatite binding sites on bone surfaces and inhibit osteoclast-mediated bone resorption. Denosumab is a

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releasing calcium and phosphate into circulation. In the kidney, PTH **decreases tubular reabsorption of phosphorus** while increasing reabsorption of calcium. Therefore, the combined effects are **increased serum calcium** and **urine phosphate levels**.

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(Choices C and D) Bisphosphonates (eg, alendronate, risedronate) are pyrophosphate analogs that attach to hydroxyapatite binding sites on bone surfaces and inhibit osteoclast-mediated bone resorption. Denosumab is a monoclonal antibody that decreases bone resorption by binding to RANK-L and blocking the interaction between RANK-L and RANK on osteoclast surfaces. These agents generally lower, rather than raise, serum calcium levels.

Educational objective:
Parathyroid hormone (PTH) causes increased bone resorption, increased serum calcium levels, and increased renal phosphate excretion. Chronically high levels of PTH increase the risk of osteoporosis. However, intermittent administration of recombinant PTH analogs (eg, teriparatide) induces a greater increase in osteoblast activity in proportion to osteoclast activity and a net increase in bone formation.

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A 15-year-old girl comes to the office for follow-up. The patient was diagnosed with Wilson disease a year ago, at which time she began penicillamine therapy. Her dysarthria and academic performance have since improved. Vital signs are normal. Laboratory results are as follows:

	Six months prior	Today
24-hr urine copper excretion (normal: <40 mcg)	500 mcg/24 hr	300 mcg/24 hr
Urinalysis	normal	protein 3+; otherwise normal
Alanine aminotransferase (SGPT)	240 U/L	140 U/L
Aspartate aminotransferase (SGOT)	200 U/L	110 U/L

Which of the following is the most likely explanation for this patient's laboratory findings?

- A. Liver cirrhosis
- B. Medication noncompliance
- C. Membranous nephropathy
- D. Renal interstitial inflammation
- E. Renal tubular injury

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Urinalysis	normal	protein 3+; otherwise normal
Alanine aminotransferase (SGPT)	240 U/L	140 U/L
Aspartate aminotransferase (SGOT)	200 U/L	110 U/L

Which of the following is the most likely explanation for this patient's laboratory findings?

- A. Liver cirrhosis (2%)
- ✗ B. Medication noncompliance (2%)
- ✓ C. Membranous nephropathy (66%)
- D. Renal interstitial inflammation (13%)
- E. Renal tubular injury (14%)

Incorrect
Correct answer

66%
Answered correctly

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Wilson disease is caused by a defective copper transporter within hepatocytes, resulting in copper accumulation in the liver, brain, eye, and other organs. **Penicillamine**, a first-line therapy for this condition, is a **copper-chelating agent** that solubilizes copper, which is then excreted in the urine. With initial treatment, urinary excretion of copper is high, as evidenced by this patient's laboratory studies from several months ago. As toxic copper stores diminish with continued chelation, urinary copper excretion decreases (although it remains elevated compared to healthy patients). In addition, although penicillamine can partially reverse liver damage, some patients continue to have mildly elevated transaminases.

Nephrotoxicity, which can occur months to years into therapy, is a potential **adverse effect** of penicillamine and most commonly presents with **nephrotic syndrome** (ie, **proteinuria**) due to **membranous nephropathy**. Pathogenesis is uncertain, but histology findings include diffuse glomerular capillary wall thickening without marked glomerular hypercellularity.

(Choices A and B) Noncompliance of penicillamine in patients with Wilson disease results in recurrence of symptoms or worsening liver (eg, cirrhosis) or renal (eg, Fanconi syndrome) manifestations. This patient has improved neurologic symptoms, academic performance, and aminotransferases, making noncompliance unlikely.

(Choice D) Interstitial nephritis, a potential adverse effect of any medication, can occasionally cause significant proteinuria. However, hematuria and pyuria would be expected on urinalysis.

(Choice E) Although tubular injury (eg, acute tubular necrosis) can result in mild proteinuria, this patient's otherwise normal urinalysis (no granular casts) and lack of risk factors (eg, ischemia, toxin exposure) make tubular injury unlikely.

Educational objective:
Penicillamine is a copper-chelating agent used as first-line treatment in Wilson disease. Adverse effects include nephrotic syndrome (ie, proteinuria) due to membranous nephropathy.

References

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Wilson disease is caused by a defective copper transporter within hepatocytes, resulting in copper accumulation in the liver, bra

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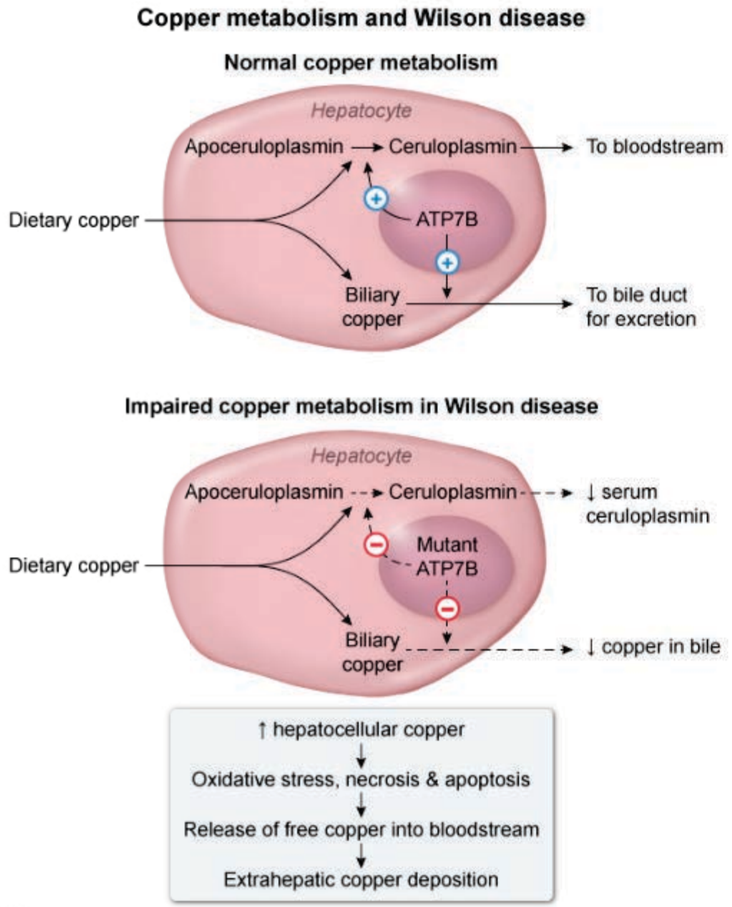
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A 2-year-old boy is brought to the office due to poor weight gain and frequent urination. His mother says he has not gained any weight since his well child visit 6 months ago, and in the last several months he has been urinating more than 10 times a day. His weight percentile has decreased from 60th percentile to 10th percentile, consistent with failure to thrive. Physical examination reveals frontal bossing. He is found to have glucosuria on urinalysis, although his serum glucose is within normal limits. Additional serum laboratory studies reveal hypophosphatemia, hypokalemia, and a normal anion gap metabolic acidosis. Which of the following structure/function combinations is most likely defective in this patient?

	Structure	Function
○ A.	Distal convoluted tubule	Generation of ammonia
○ B.	Distal convoluted tubule	Reabsorption of bicarbonate
○ C.	Distal convoluted tubule	Secretion of hydrogen ions
○ D.	Proximal convoluted tubule	Generation of ammonia
○ E.	Proximal convoluted tubule	Reabsorption of bicarbonate
○ F.	Proximal convoluted tubule	Secretion of hydrogen ions

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	Structure	Function	
	A. Distal convoluted tubule	Generation of ammonia	(2%)
✗	B. Distal convoluted tubule	Reabsorption of bicarbonate	(5%)
	C. Distal convoluted tubule	Secretion of hydrogen ions	(9%)
	D. Proximal convoluted tubule	Generation of ammonia	(7%)
✓	E. Proximal convoluted tubule	Reabsorption of bicarbonate	(64%)
	F. Proximal convoluted tubule	Secretion of hydrogen ions	(10%)

Incorrect
Correct answer
E

64%
Answered correctly

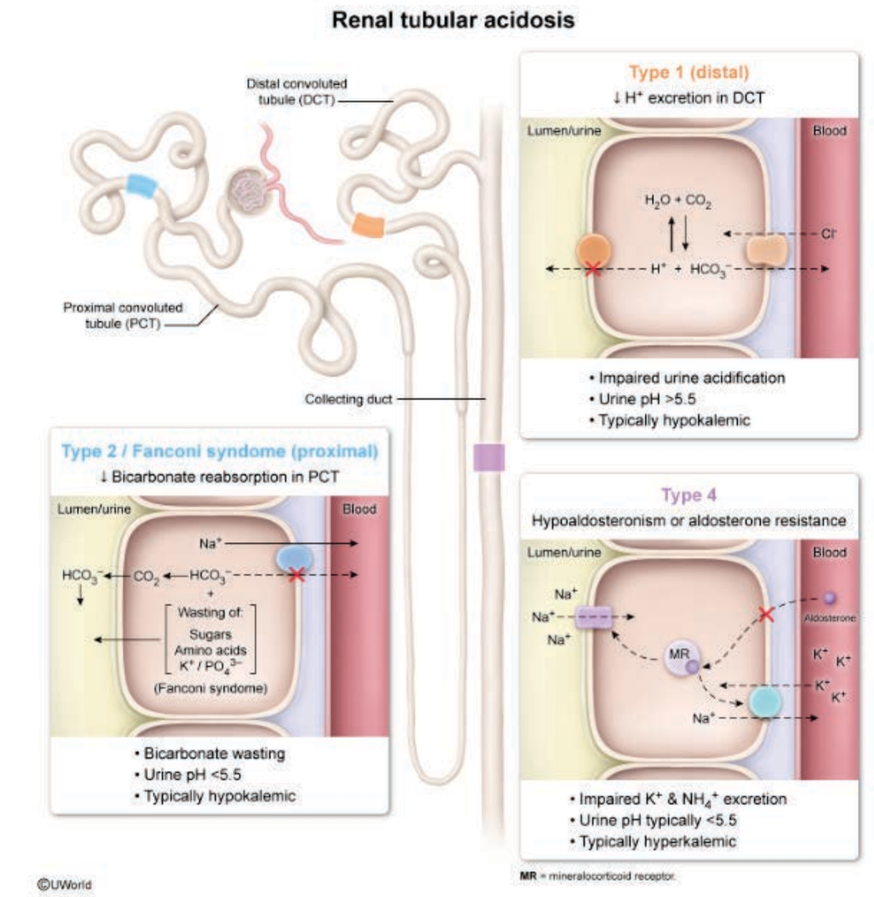
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Explanation

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• Urine pH typically <5.5
• Typically hyperkalemic

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This patient's glycosuria with normal serum glucose in combination with normal anion gap metabolic acidosis, hypokalemia, and hypophosphatemia is highly suggestive of impaired proximal tubular reabsorption. The **proximal convoluted tubule** is responsible for reabsorption of bicarbonate in addition to amino acids, phosphate, glucose, water, and potassium. Impaired bicarbonate reabsorption can occur as an isolated defect (renal tubular acidosis [RTA] type 2) or as part of a more generalized proximal tubular dysfunction (**Fanconi syndrome**):

- **Loss of bicarbonate** causes persistent acidosis.
- **Hypophosphatemia** leads to rickets (eg, frontal bossing, leg bowing).
- **Glucosuria** contributes to polyuria (impaired renal concentrating ability also contributes). Serum glucose levels are normal, as seen here, because they are tightly regulated by multiple mechanisms (eg, insulin, glucagon) that are independent of renal reabsorption.
- **Hypokalemia** can lead to constipation and muscle weakness.
- Aminoaciduria, contributing to growth failure.

(Choices A and D) The proximal tubule is also responsible for the generation of ammonia (NH_3). Hypoaldosteronism or aldosterone resistance (RTA type 4, most commonly seen in adults with diabetes) can disrupt this process by inhibiting production of NH_3 in the proximal tubule, resulting in reduced ammonium (NH_4^+) excretion and metabolic acidosis. This patient's hypokalemia and hypophosphatemia are inconsistent with this diagnosis.

(Choices B, C, and F) Hydrogen ions (H^+) are primarily secreted into the urine from the distal convoluted tubule. Failure of this process (RTA type 1) leads to decreased distal acid secretion and metabolic acidosis, but phosphate and glucose would be normal.

Educational objective:
Defects in either the proximal or distal convoluted tubule (eg, bicarbonate loss, acid retention) can result in a normal anion gap metabolic acidosis. However, the proximal tubule is responsible for reabsorption of glucose

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glucose, water, and potassium. Impaired bicarbonate reabsorption can occur as an isolated defect (renal tubular acidosis [RTA] type 2) or as part of a more generalized proximal tubular dysfunction (**Fanconi syndrome**):

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Educational objective:
Defects in either the proximal or distal convoluted tubule (eg, bicarbonate loss, acid retention) can result in a normal anion gap metabolic acidosis. However, the proximal tubule is responsible for reabsorption of glucose, amino acids, and phosphate in addition to bicarbonate; therefore, generalized proximal tubular dysfunction (Fanconi syndrome) can also cause failure to thrive, glucosuria, and rickets.

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- Typically hypokalemic
- Impaired K^+ & NH_4^+ excretion
- Urine pH typically <5.5
- Typically hyperkalemic

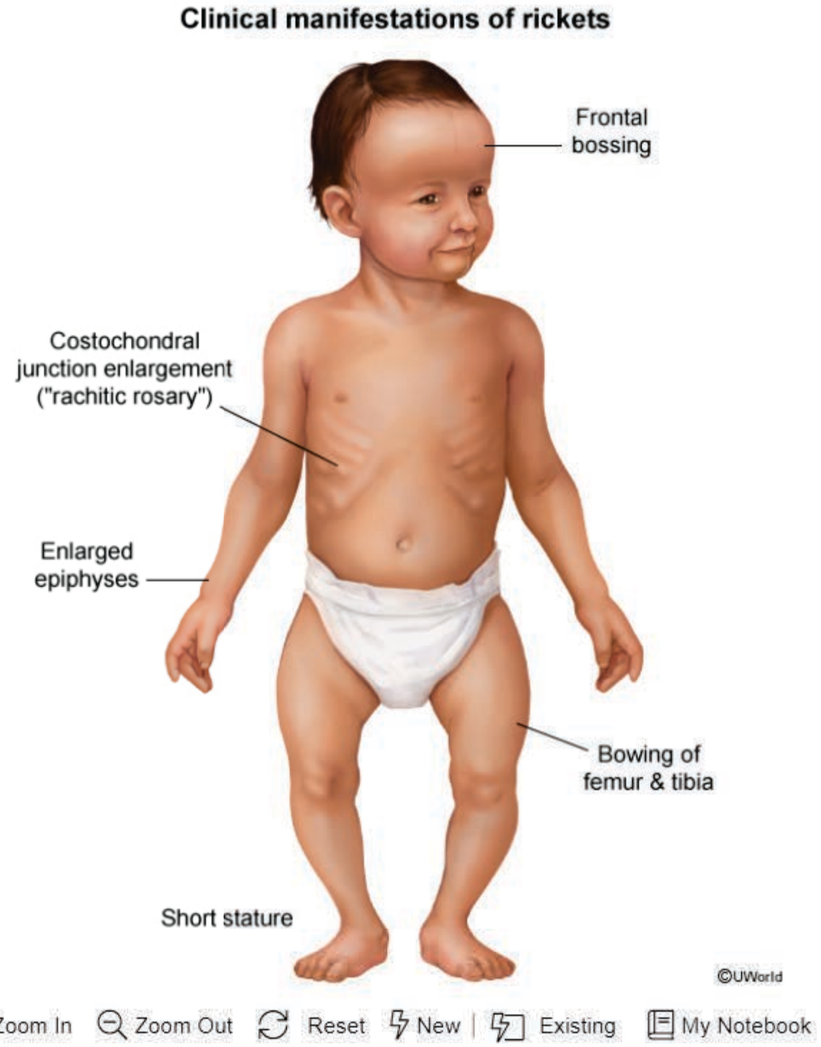
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A 36-year-old man is brought to the emergency department due to confusion, nausea, and decreased arousal. He is unable to answer questions and no other history is available. Temperature is 36.7 C (98.1 F), pulse is 86/min, and respirations are 22/min. Arterial blood gas and serum chemistry results are as follows:

pH	7.25
PaO_2	96 mm Hg
$PaCO_2$	28 mm Hg
Sodium	136 mEq/L
Potassium	3.6 mEq/L
Chloride	90 mEq/L
Bicarbonate	12 mEq/L
Blood urea nitrogen	30 mg/dL
Creatinine	1.2 mg/dL

Which of the following is the most likely primary acid-base disorder in this patient?

- A. Anion gap metabolic acidosis
- B. Metabolic alkalosis
- C. Nonanion gap metabolic acidosis
- D. Respiratory acidosis
- E. Respiratory alkalosis

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Blood urea nitrogen	30 mg/dL
Creatinine	1.2 mg/dL

Which of the following is the most likely primary acid-base disorder in this patient?

- ✓ A. Anion gap metabolic acidosis (88%)
- ✗ B. Metabolic alkalosis (0%)
- C. Nonanion gap metabolic acidosis (7%)
- D. Respiratory acidosis (2%)
- E. Respiratory alkalosis (0%)

Incorrect
Correct answer
A

88%
Answered correctly

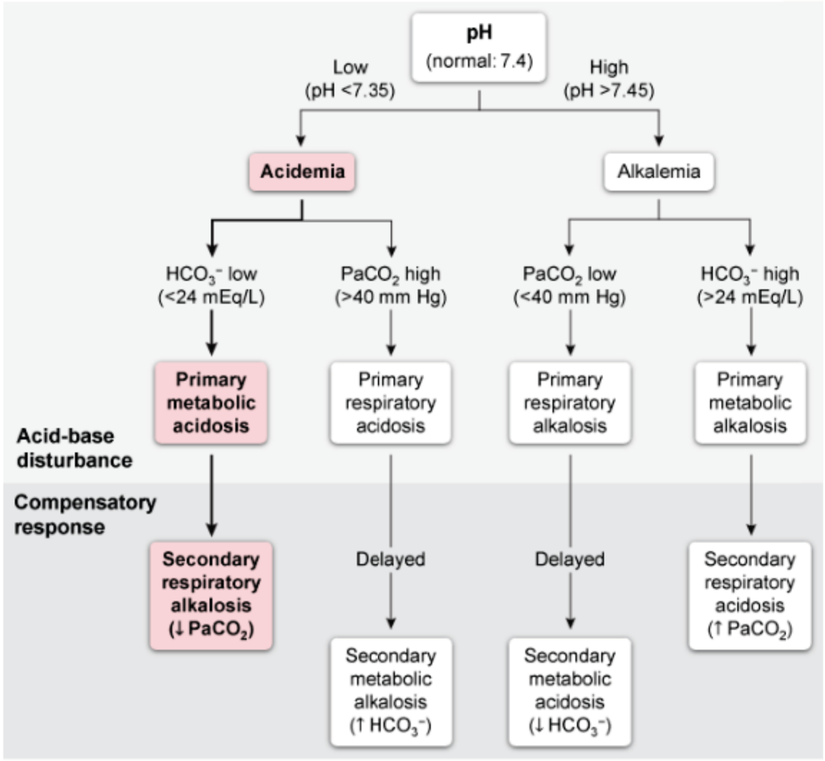
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Arterial blood gas interpretation of acid-base disorders



*The normal ranges for $PaCO_2$ and HCO_3^- vary slightly around 40 mm Hg and 24 mEq/L.
For simplicity, these numbers should be used as a normal baseline for acid-base calculations.

HCO_3^- = bicarbonate; **$PaCO_2$** = partial pressure of carbon dioxide in arterial blood.

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*The normal ranges for $PaCO_2$ and HCO_3^- vary slightly around 40 mm Hg and 24 mEq/L.

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Arterial blood gas analysis can be particularly helpful in the evaluation of **encephalopathy** (eg, confusion, decreased arousal) when a history cannot be obtained. If present, acid-base abnormalities can help guide further diagnosis and management. Acid-base status is best evaluated in a stepwise fashion:

1. Evaluate the **pH**: This patient's low pH of 7.25 indicates **acidemia** (ie, <7.35).

2. Identify the **primary process**: Analyze the metabolic component of acid-base balance, serum HCO_3^- (normal: 24 mEq/L), and the respiratory component, $PaCO_2$ (normal: 40 mm Hg). The parameter shifted in the direction that explains the change in pH represents the primary disorder. This patient's serum HCO_3^- of 12 mEq/L is low (shifted toward acidity) **(Choice B)**, indicating primary **metabolic acidosis**.

3. Determine the **compensation**: Primary metabolic disorders are quickly compensated via adjustments in alveolar ventilation and CO_2 removal (eg, hyperventilation in this patient). The expected compensation for this patient's primary metabolic acidosis is a secondary respiratory alkalosis with a $PaCO_2$ of 24-28 mm Hg (estimated using Winters formula). This patient's $PaCO_2$ of 28 mm Hg is within the expected range, indicating that there is no additional *primary* respiratory disorder (ie, **appropriate** compensation).

This patient therefore has a primary metabolic acidosis without an additional primary disorder. The next step in further characterizing metabolic acidosis is calculation of the anion gap, which consists of unmeasured anions that are normally present in the serum. The anion gap is approximately equal to ($Na^+ - [HCO_3^- + Cl^-]$); this patient's anion gap of 34 mEq/L is significantly higher than normal (ie, 10-14 mEq/L) **(Choice C)**. Because of the large number of etiologies of high **anion gap metabolic acidosis** (eg, toxic alcohol ingestion), further work-up is often necessary.

(Choice D) Although primary respiratory acidosis would also cause a pH <7.35, a high $PaCO_2$ with a compensatory rise in HCO_3^- would be expected.

(Choice E) Primary respiratory alkalosis is characterized by a pH >7.45 (ie, alkalemia), rather than acidemia.

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(Choice E) Primary respiratory alkalosis is characterized by a pH >7.45 (ie, alkalemia), rather than acidemia.

Educational objective:
Primary metabolic acidosis is characterized by a pH <7.35 (ie, acidemia), low serum HCO_3^-, and a compensatory low $PaCO_2$. An anion gap ($Na^+ - [HCO_3^- + Cl^-]$) above normal (ie, 10-14 mEq/L) indicates a high anion gap metabolic acidosis.

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mEq/L is low (shifted toward acidity) **(Choice B)**, indicating primary **metabolic acidosis**.

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Appropriate compensatory $PaCO_2$ or HCO_3^- changes in acid-base disorders	
Metabolic acidosis (acute or chronic)	Expected $PaCO_2 = (1.5 \times HCO_3^-) + 8 \pm 2$ (Winters formula)
Metabolic alkalosis (acute or chronic)	~7 mm Hg ↑ in $PaCO_2$ per 10 mEq/L ↑ in HCO_3^-
Respiratory acidosis (chronic only*)	~4 mEq/L ↑ in HCO_3^- per 10 mm Hg ↑ in $PaCO_2$
Respiratory alkalosis (chronic only*)	~4 mEq/L ↓ in HCO_3^- per 10 mm Hg ↓ in $PaCO_2$
*Compensation for respiratory disturbances is minimal in the acute setting. The full level of chronic compensation is achieved after ~72 hr. For simplicity, normal baseline $PaCO_2$ & HCO_3^- should be considered 40 mm Hg & 24 mEq/L, respectively.	

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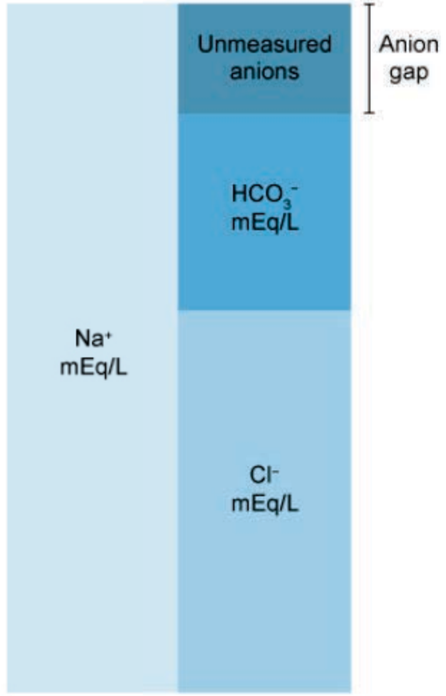
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mEq/L is low (shifted toward acidity) **(Choice B)**, indicating primary **metabolic acidosis**.

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Calculation of the anion gap



Anion gap = $Na^+ - (Cl^- + HCO_3^-)$
Normal: 10-14 mEq/L

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mEq/L is low (shifted toward acidity) **(Choice B)**, indicating primary **metabolic acidosis**.

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Anion gap metabolic acidosis	
Calculation	Anion gap = sodium – (chloride + bicarbonate) (normal: 10-14 mEq/L)
Common causes Mnemonic: MUDPILES	• Methanol • Uremia • Diabetic ketoacidosis • Propylene glycol/paraldehyde • Isoniazid/iron • Lactic acidosis • Ethylene glycol (antifreeze) • Salicylate (aspirin)

New | Existing | My Notebook

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A 23-year-old man with type 1 diabetes mellitus is brought to the emergency department due to confusion and weakness. Symptoms began 2 days ago with mild diarrhea. The patient has missed several doses of insulin because his appetite has been poor. On examination, his breath has a fruity odor. This patient is most likely to demonstrate which of the following urine chemistry patterns?

	pH	HCO_3^-	NH_4^+
○ A.	↑	↑	↑
○ B.	↑	↓	↑
○ C.	↓	↓	↓
○ D.	↓	↓	↑
○ E.	↓	↑	↑

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	pH	HCO_3^-	NH_4^+	
A.	↑	↑	↑	(7%)
✗ B.	↑	↓	↑	(4%)
C.	↓	↓	↓	(12%)
✓ D.	↓	↓	↑	(63%)
E.	↓	↑	↑	(12%)

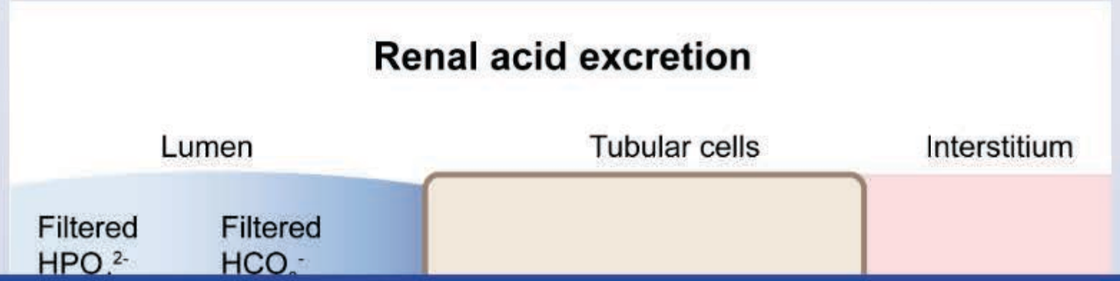
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Correct answer
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63%
Answered correctly

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Explanation



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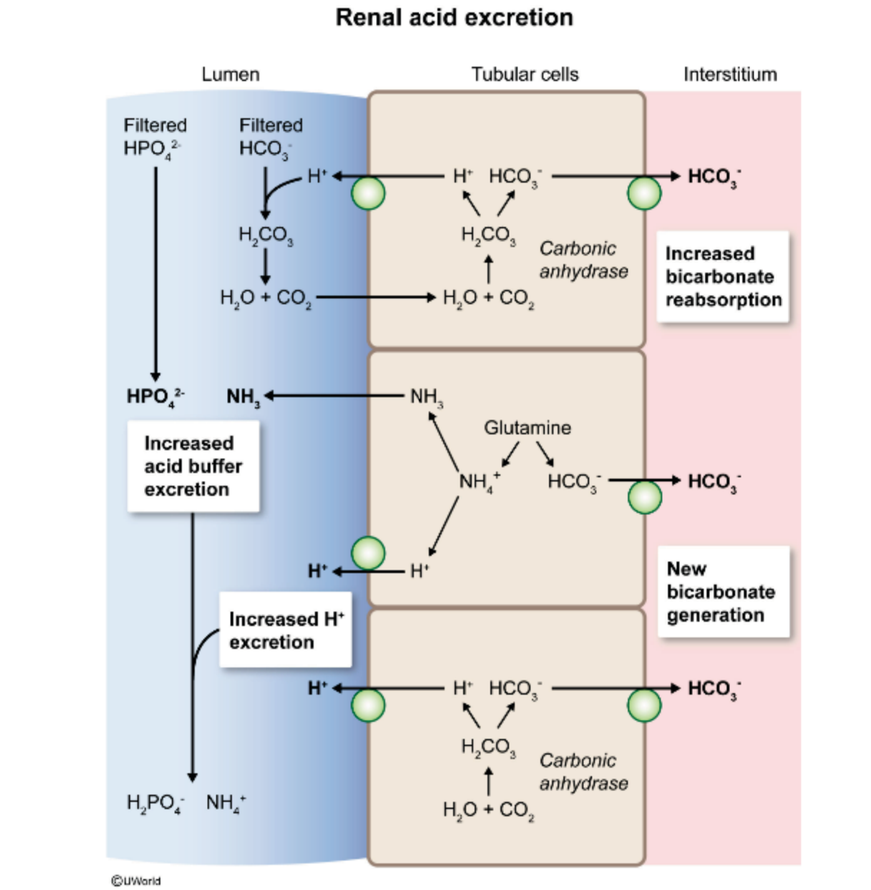
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bicarbonate



This patient with type 1 diabetes mellitus has been nonadherent with his insulin regimen due to poor appetite, which has led to **diabetic ketoacidosis**. Complete insulin deficiency leads to excessive generation of organic anions (eg, ketone bodies that smell fruity), thereby causing **metabolic acidosis** (ie, decreased serum bicarbonate [HCO_3^-] and pH).

The kidneys can normally compensate somewhat for metabolic acidosis by increasing renal acid excretion. The major mechanisms of increased renal acid excretion include:

- **Increased H^+ secretion**: Intracellular acidosis leads to a direct increase in H^+ secretion via increased activity of the apical Na^+/H^+ exchanger.
- **Increased HCO_3^- reabsorption**: Carbonic anhydrase in the proximal tubular lumen facilitates reabsorption of filtered HCO_3^-. Each reabsorbed HCO_3^- is equivalent to the secretion of one H^+. In metabolic acidosis, HCO_3^- is completely reabsorbed from the tubular fluid.
- Increased acid buffer excretion: Urinary acid buffers, hydrogen phosphate (HPO_4^{2-}) and ammonia (NH_3), are used to trap H^+ in the lumen in the form of **$H_2PO_4^-$** and **NH_4^+**, vastly increasing the amount of acid that can be **excreted** in the urine. With chronic acidosis, proximal tubular cells greatly increase NH_3 production to increase acid excretion capacity.

Educational objective:
The kidneys can normally compensate somewhat for metabolic acidosis by completely reabsorbing filtered bicarbonate (HCO_3^-) and excreting excess H^+ in the urine. Most of the excreted H^+ is buffered by phosphate ($H_2PO_4^-$) and ammonium (NH_4^+).

Physiology	Renal, Urinary Systems & Electrolytes	Diabetic ketoacidosis
Subject	System	Topic

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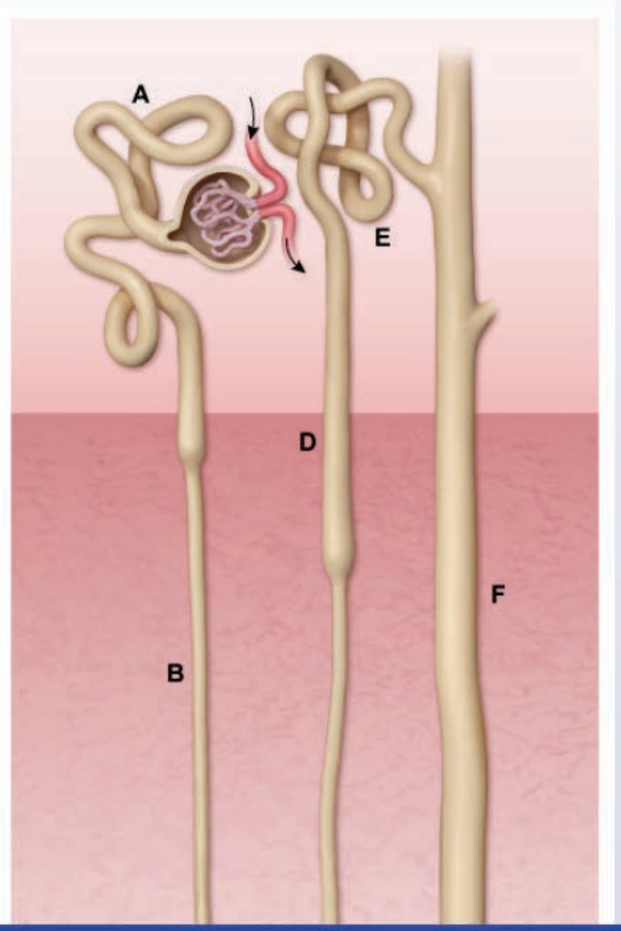
Nephrologists at a research hospital are investigating the physiologic changes that occur in diabetes insipidus. The group develops a technique that permits sampling of tubular urine in experimental animals with physiology similar to that of humans. The animals then undergo hypophysectomy, after which tubular fluid samples are obtained from multiple sites throughout the nephron. In the absence of antidiuretic hormone, fluid from which of the following sampling sites is most likely to have the highest osmolarity?

- A. A
- B. B
- C. C
- D. D
- E. E
- F. F

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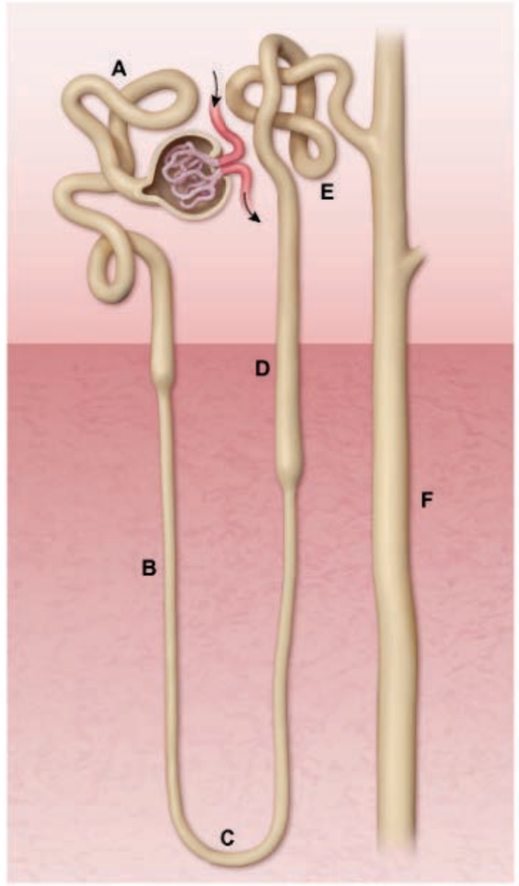
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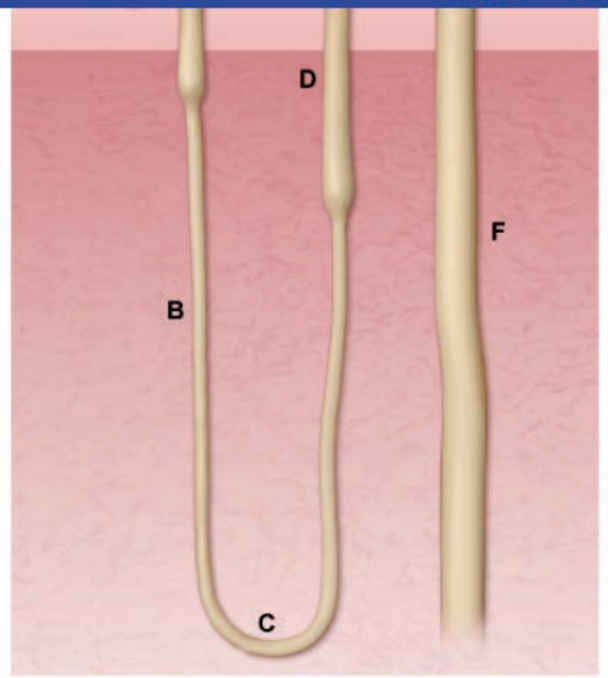
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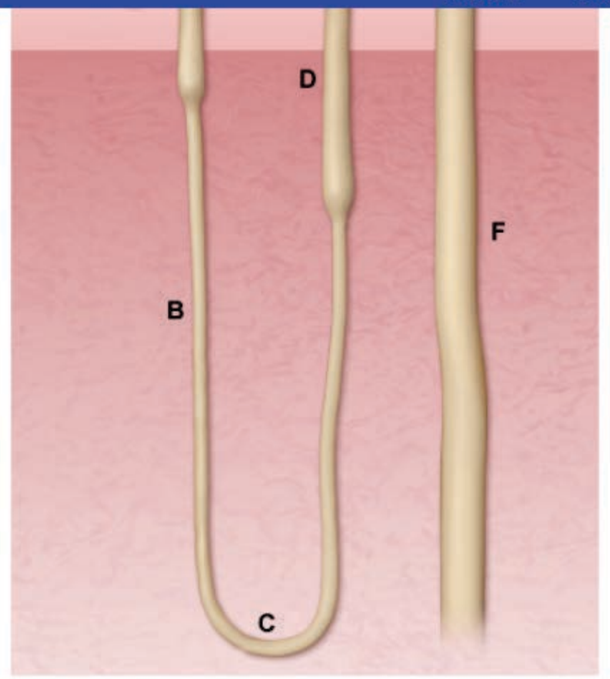
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- A. A
- B. B
- C. C
- D. D
- E. E
- F. F

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- A. A (4%)
- B. B (7%)
- ✓ C. C (59%)
- D. D (8%)
- E. E (6%)
- F. F (13%)

Correct

59%
Answered correctly

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Time Spent

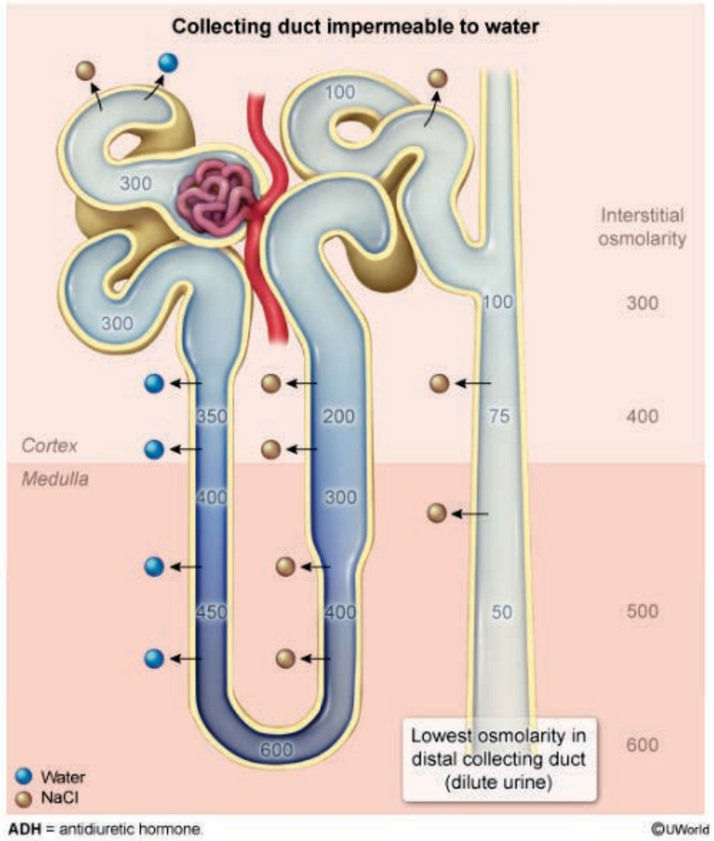
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Correct
59% Answered correctly
15 secs Time Spent
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Tubular fluid osmolarity in the setting of low ADH



ADH = antidiuretic hormone.

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Tubular fluid osmolarity varies along the different segments of the nephron depending on each segment's permeability to water, the osmolarity of the renal interstitium, and the presence or absence of antidiuretic hormone (ADH):

1. In the proximal tubule, water is passively reabsorbed along with active transport of solutes into the interstitium. Fluid in the proximal tubule lumen is therefore isoosmotic with plasma **(Choice A)**.

2. The descending limb of the loop of Henle is permeable to water, but not solutes. As this segment of the nephron descends into the medullary interstitium, water moves down its concentration gradient from the lumen into the highly osmotic medulla. No reabsorption of electrolytes occurs in this segment, so the fluid in the lumen becomes hypertonic **(Choice B)**. However, tubular fluid will be the **most concentrated** at the **bottom of the loop** of Henle where interstitial osmolality is the greatest.

3. The thick ascending limb of the loop of Henle is impermeable to water. In this portion of the nephron, electrolytes are actively resorbed by the $Na^+/K^+/2Cl^-$ cotransporter, causing the osmolarity of the tubular fluid to decrease and become hypotonic **(Choice D)**.

4. Reabsorption of solutes continues to occur in the distal convoluted tubule through the action of the NaCl symporter. Because the early distal convoluted tubule is impermeable to water, tubular fluid increases in hypotonicity in this segment of the nephron **(Choice E)**.

5. The water permeability of the collecting ducts depends on the presence of ADH. In the **absence of antidiuretic hormone** (ADH) (eg, overhydration, diabetes insipidus), the collecting ducts are impermeable to water, even when passing through high-osmolarity regions within the medullary concentration gradient. As solutes continue to be removed, tubular fluid in this segment can become as hypotonic as 50 mOsm/L, producing a very **dilute urine**.

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the lumen becomes hypertonic **(Choice B)**. However, tubular fluid will be the **most concentrated** at the **bottom of the loop** of Henle where interstitial osmolality is the greatest.

3. The thick ascending limb of the loop of Henle is impermeable to water. In this portion of the nephron, electrolytes are actively resorbed by the $Na^+/K^+/2Cl^-$ cotransporter, causing the osmolarity of the tubular fluid to decrease and become hypotonic **(Choice D)**.

4. Reabsorption of solutes continues to occur in the distal convoluted tubule through the action of the NaCl symporter. Because the early distal convoluted tubule is impermeable to water, tubular fluid increases in hypotonicity in this segment of the nephron **(Choice E)**.

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(Choice F) When ADH levels are high (eg, dehydration), the collecting duct is highly permeable to water. Water leaves the tubular fluid driven by the high osmolarity of the medullary interstitium, and hypertonic urine is formed (up to 1200 mOsm/L). However, in this experiment the hypophysectomized animals are unable to produce ADH and will have dilute urine.

Educational objective:
Antidiuretic hormone (ADH) acts primarily on the collecting ducts, increasing their permeability to water. In the absence of ADH, the tubular fluid is most concentrated at the junction between the descending and ascending limbs of the loop of Henle and most dilute in the collecting ducts.

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the lumen becomes hypertonic **(Choice B)**. However, tubular fluid will be the **most concentrated** at the

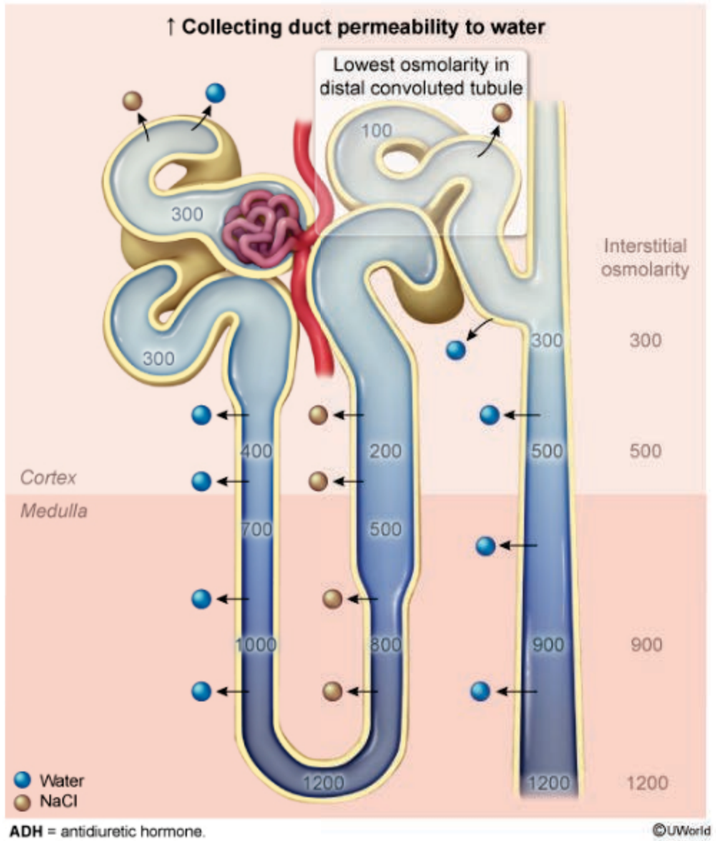
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3.

4.

5.

Tubular fluid osmolarity in the setting of high ADH



ADH = antidiuretic hormone.

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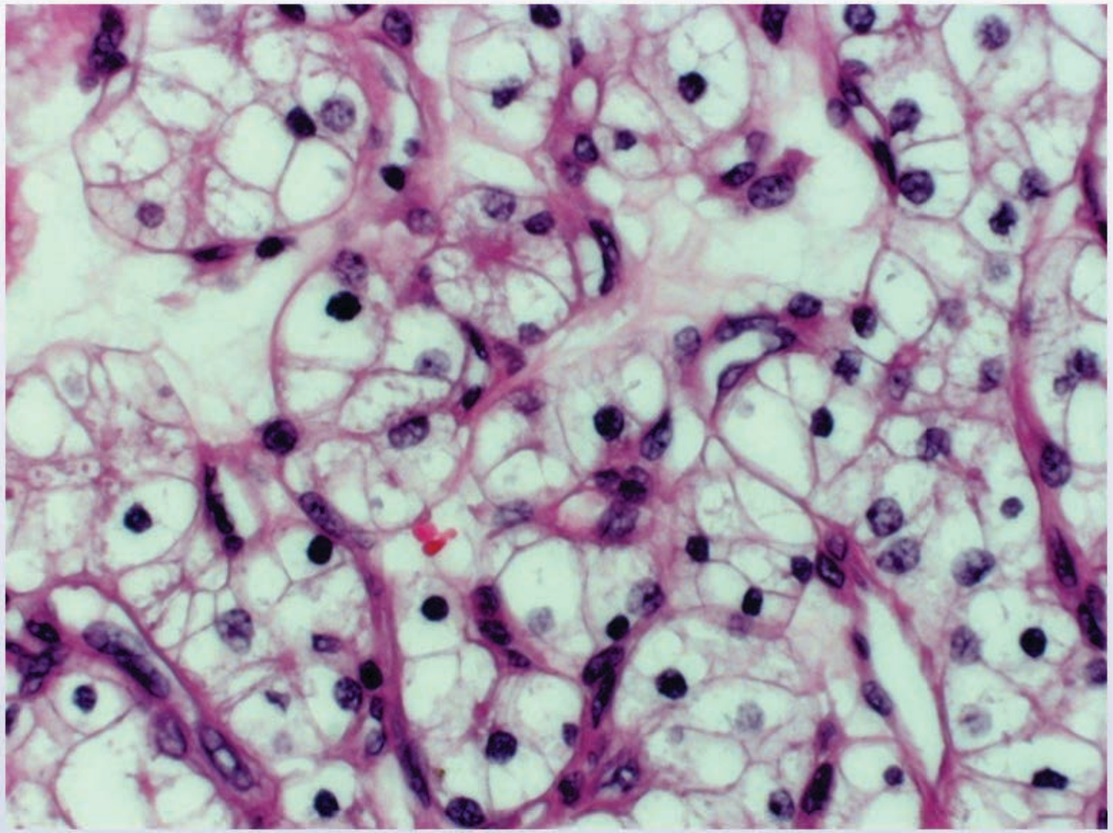
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limbs of the loop of Henle and most dilute in the collecting ducts.

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A 63-year-old man comes to the emergency department due to fever and loss of appetite. He also has chest pain with deep breaths. The patient has never had regular medical care and his medical history is unknown. He has smoked half a pack of cigarettes daily for 30 years. Laboratory evaluation shows a hematocrit of 56%. Chest imaging shows multiple round lesions in both lungs. Biopsy of one of the lesions reveals the microscopic findings shown below.

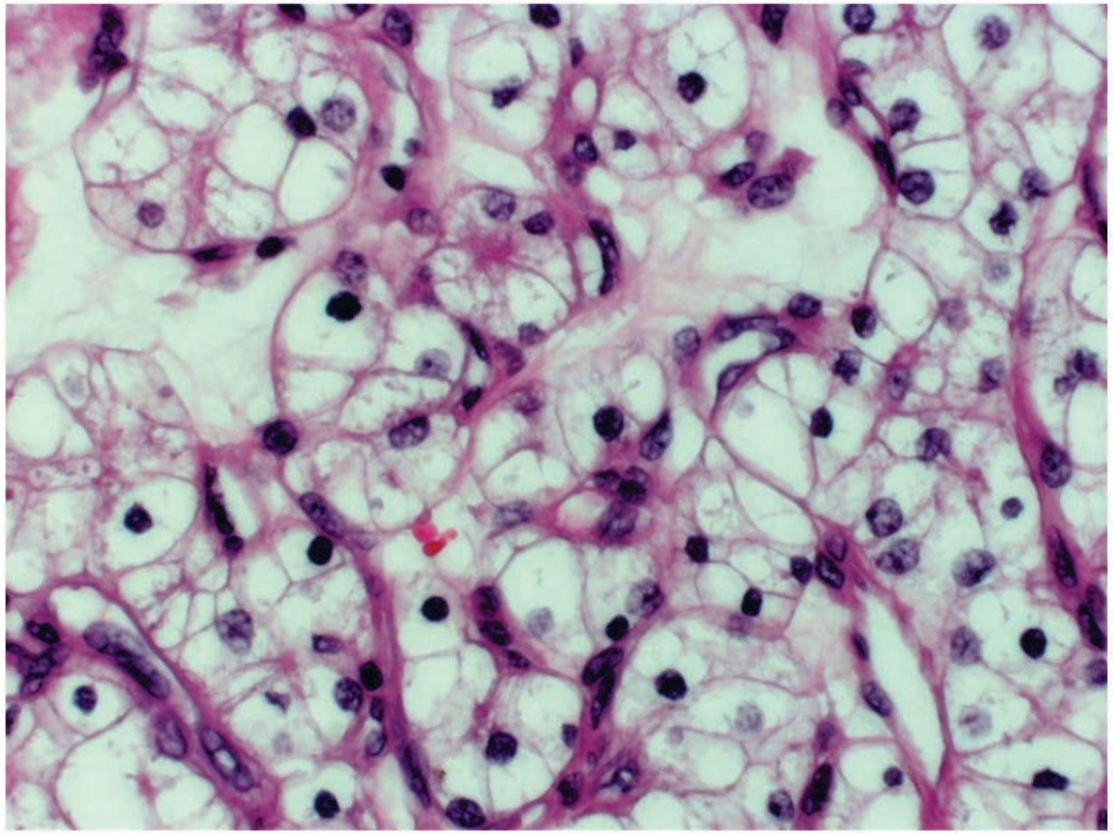


This patient's metastatic disease most likely originated from which of the following organs?

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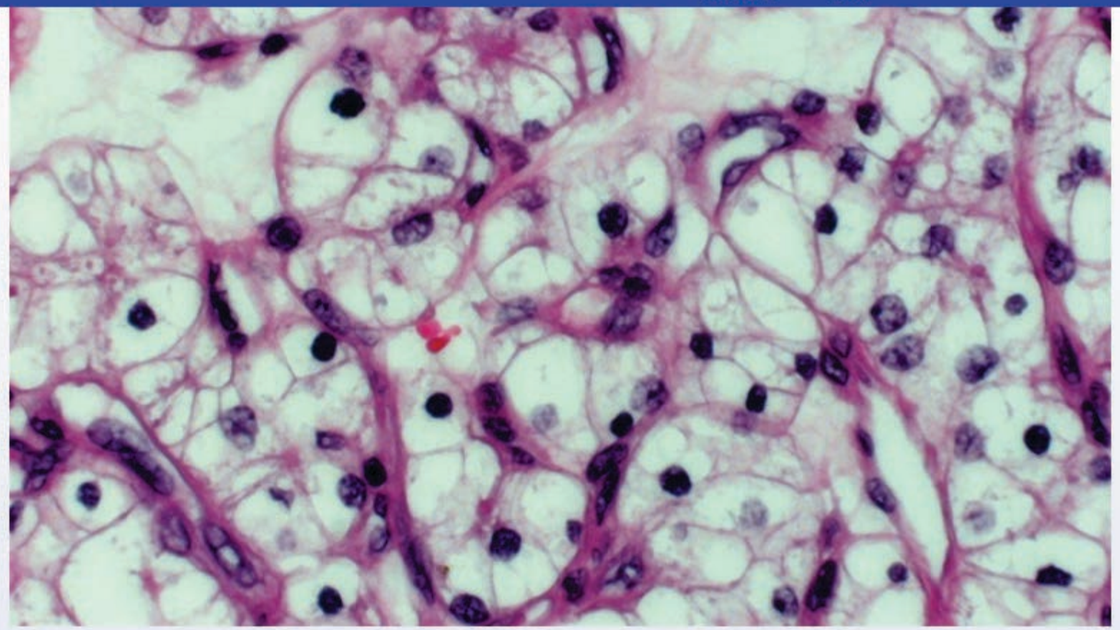
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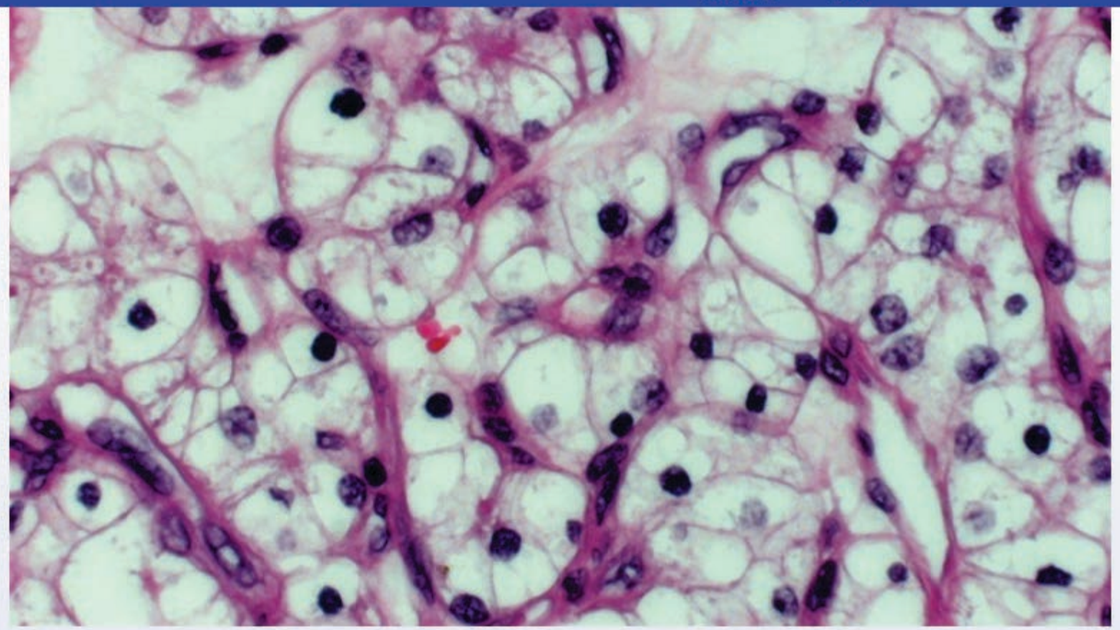


This patient's metastatic disease most likely originated from which of the following organs?

- A. Bone
- B. Brain
- C. Colon
- D. Kidney
- E. Stomach
- F. Testis

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This patient's metastatic disease most likely originated from which of the following organs?

- A. Bone (5%)
- B. Brain (0%)
- C. Colon (7%)
- ✓ D. Kidney (78%)
- E. Stomach (3%)
- F. Testis (4%)

Correct

78% Answered correctly

16 secs Time Spent

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Explanation

Renal cell carcinoma	
Common presentation	• Asymptomatic (most common) • Hematuria, flank pain, palpable abdominal mass
Histopathology (clear cell)	• Rounded polygonal or cuboidal cells • Abundant clear or yellow cytoplasm
Common metastatic site	• Lungs ("cannonball metastases") • Bone (osteolytic)
Paraneoplastic syndromes	• Polycythemia (erythropoietin production) • Hypercalcemia (parathyroid hormone-related peptide production) • Hormone production (eg, ACTH, renin)

This patient has fevers, anorexia, and polycythemia. His evaluation shows multiple round lung lesions with microscopy revealing rounded polygonal cells with **abundant clear cytoplasm**. This presentation is consistent with metastatic clear cell carcinoma, the most common subtype of **renal cell carcinoma** (RCC). The cytoplasm appears clear due to the high glycogen and lipid content of the tumor. For the same reason, this neoplasm is often golden-yellow on macroscopic examination.

Patients with RCC are often asymptomatic; the classic triad of hematuria, flank pain, and palpable abdominal mass occur together in less than 10% of cases, often late in the course of the disease. **Nonspecific symptoms** such as fever and weight loss are more common. Paraneoplastic syndromes, including polycythemia (constitutive secretion of erythropoietin) and hypercalcemia (synthesis of parathyroid hormone-related protein), can also occur.

Renal cell carcinoma is often **detected incidentally** since localizing symptoms only develop in advanced disease; metastases are often discovered earlier than the primary neoplasm. RCC most commonly **metastasizes to the**

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Common metastatic site	• Bone (osteolytic)
Paraneoplastic syndromes	• Polycythemia (erythropoietin production) • Hypercalcemia (parathyroid hormone-related peptide production) • Hormone production (eg, ACTH, renin)

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Renal cell carcinoma is often **detected incidentally** since localizing symptoms only develop in advanced disease; metastases are often discovered earlier than the primary neoplasm. RCC most commonly **metastasizes to the lungs**, where it often presents as large, rounded, well-circumscribed "cannonball" metastases. Osteolytic bone lesions and liver metastases also occur frequently.

(Choice A) Osteosarcoma frequently metastasizes to the lungs, but most patients have localized pain at the primary site (eg, distal femur), and polycythemia is unexpected. Histologically, pleomorphic malignant tumor cells with osteoid matrix production would be seen.

(Choice B) Primary brain neoplasms usually metastasize within the CNS; although they can rarely metastasize outside the nervous system, they would not be associated with polycythemia.

(Choices C and E) Colon and stomach cancers commonly metastasize to the lungs. Microscopy of diffuse-type

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(Choice B) Primary brain neoplasms usually metastasize within the CNS; although they can rarely metastasize outside the nervous system, they would not be associated with polycythemia.

(Choices C and E) Colon and stomach cancers commonly metastasize to the lungs. Microscopy of diffuse-type gastric adenocarcinoma demonstrates signet ring cells with clear cytoplasmic mucin and eccentric nuclei (resembling a signet ring). Colonic adenocarcinoma forms glands and tubules. However, patients typically develop anemia due to occult bleeding, not polycythemia.

(Choice F) Testicular cancer also commonly metastasizes to the lung, but patients typically have a testicular mass. β-hCG or alpha-fetoprotein are often elevated; however, hematocrit elevations are unexpected. Histology varies by malignancy.

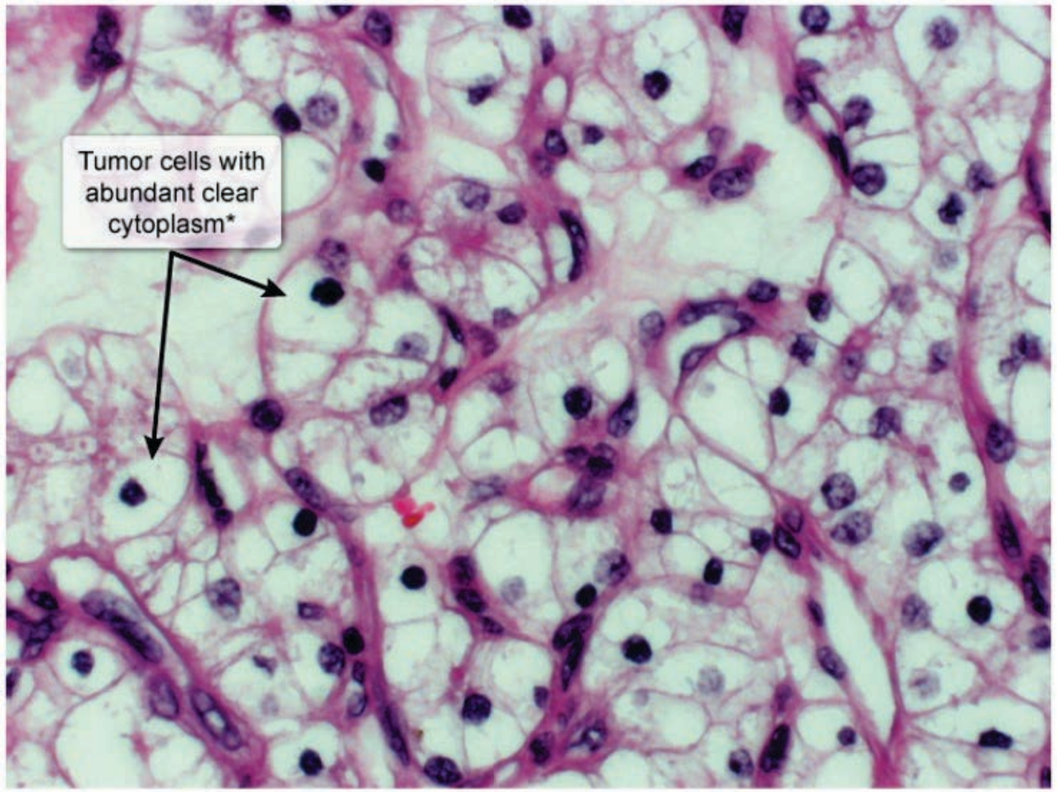
Educational objective:
Clear cell carcinoma is the most common subtype of renal cell carcinoma and is composed of large, rounded, or polygonal cells with clear cytoplasm. These tumors are often detected incidentally at an advanced stage; the lung is the most common site for metastasis, followed by osteolytic bone and liver.

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Common metastatic site	• Bone (osteolytic)

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Clear cell renal cell carcinoma



*Rich in glycogen and lipid

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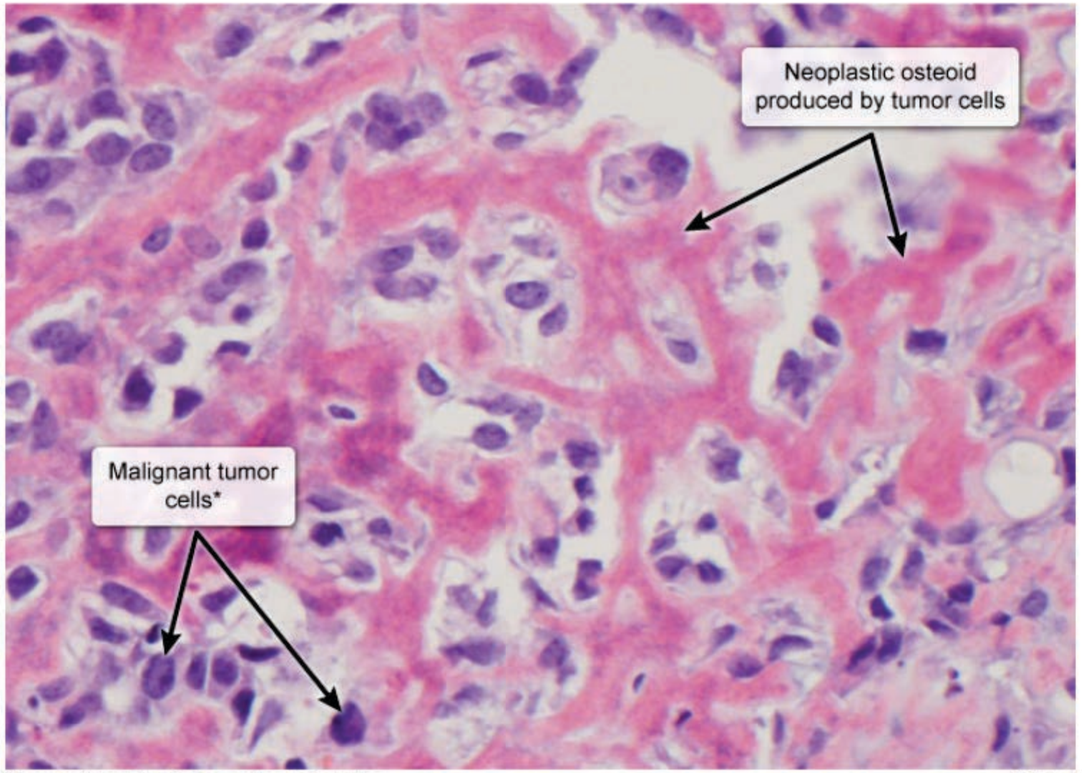
(Choices C and E) Colon and stomach cancers commonly metastasize to the lungs. Microscopy of diffuse-type

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Common metastatic site	• Bone (osteolytic)

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Osteosarcoma



*Pleomorphic cells with hyperchromatic nuclei.

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(Choices C and E) Colon and stomach cancers commonly metastasize to the lungs. Microscopy of diffuse-type

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golden-yellow on macroscopic examination.

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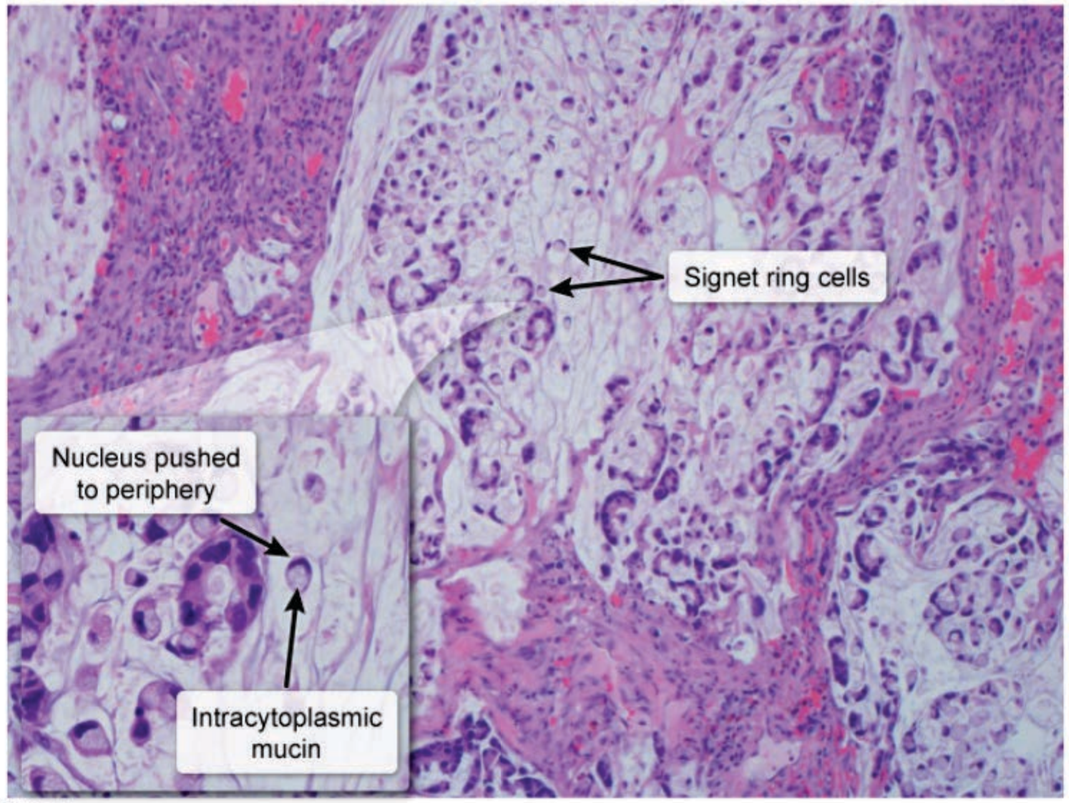
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Clear cell carcinoma is the most common subtype of renal cell carcinoma and is composed of large, rounded, or

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Gastric adenocarcinoma



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golden-yellow on macroscopic examination.

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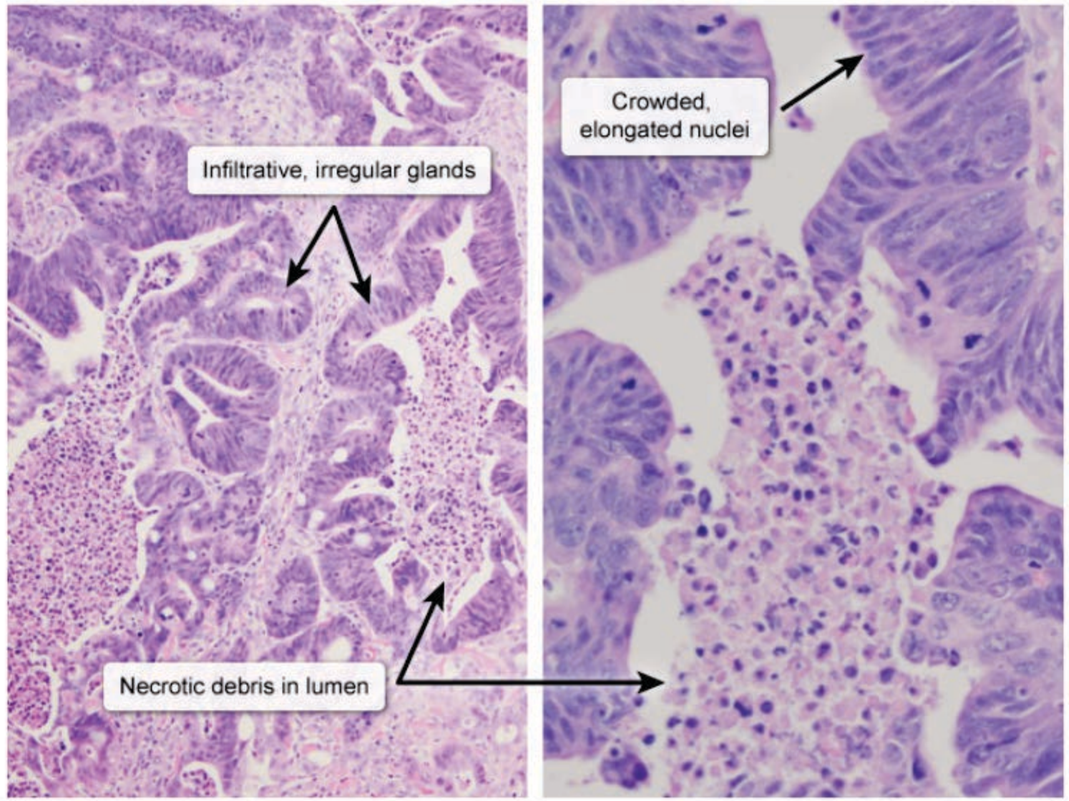
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Clear cell carcinoma is the most common subtype of renal cell carcinoma and is composed of large, rounded, or

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Colorectal adenocarcinoma



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A 64-year-old man comes to the office for follow-up. He has a history of chronic kidney disease due to hypertensive and diabetic nephropathy. Six months ago, he developed significant fatigue and exercise intolerance. Evaluation at that time revealed normocytic anemia and normal serum iron studies so recombinant erythropoietin was initiated. Today, the patient states that his symptoms have significantly improved. Laboratory evaluation reveals a hemoglobin of 12 g/dL. If the erythropoietin treatment is continued, this patient is at greatest risk for which of the following complications?

- A. Autoimmune hemolysis
- B. Bone marrow fibrosis
- C. Gallstone formation
- D. Iron overload
- E. Venous thrombosis

Submit

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- A. Autoimmune hemolysis (1%)
- ✗ B. Bone marrow fibrosis (7%)
- C. Gallstone formation (4%)
- D. Iron overload (12%)
- ✓ E. Venous thrombosis (74%)

Incorrect
Correct answer
E

74%
Answered correctly

05 secs
Time Spent

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Explanation

Erythropoietin (EPO) promotes the survival, differentiation, and proliferation of immature erythrocytes. It is produced by interstitial fibroblasts near the peritubular capillaries of the kidney in response to hypoxia; **deficiency** often occurs in the setting of chronic kidney disease due to inflammatory damage to the peritubular interstitial fibroblasts.

Patients with EPO deficiency generally present with **normocytic anemia**, low reticulocyte count, and iron studies

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Patients with EPO deficiency generally present with **normocytic anemia**, low reticulocyte count, and iron studies similar to those seen in anemia of chronic disease (eg, low serum iron, low/normal total iron-binding capacity). Treatment with **recombinant EPO** restores the stimulus for erythropoiesis, **increases hemoglobin**, and improves tissue oxygen delivery. However, **prolonged use** of EPO can lead to serious morbidity, including the following:

- **Thromboembolism:** EPO increases blood viscosity and triggers the release of proinflammatory cytokines from the endothelium, which increases the risk for thromboembolism. It also promotes the release of procoagulant proteins such as von Willebrand factor and plasminogen activator inhibitor-1.
- **Hypertension:** EPO increases systemic vascular resistance, possibly due to activation of erythropoietin receptors on vascular endothelial and smooth muscle cells. This can result in hypertensive encephalopathy and increased risk of **cardiovascular events** (eg, stroke, myocardial infarction).

To avoid morbidity, most studies recommend **cessation** of recombinant EPO once hemoglobin improves to **12-13 g/dL**; attempting to increase hemoglobin >13 g/dL increases the risk of adverse effects and death.

(Choice A) Autoantibodies can form against recombinant EPO, which limits its efficacy. However, recombinant EPO does not typically trigger autoantibodies against erythrocytes; therefore, hemolytic anemia would be atypical.

(Choice B) Recombinant EPO may worsen malignancy due to the promotion of vascular growth. It does not typically cause myelofibrosis or myeloproliferative disorders. However, these conditions may be triggered by the use of granulocyte colony–stimulating hormone due to excessive stimulation of granulocyte stem cells.

(Choice C) The use of recombinant EPO does not usually increase bilirubin and does not typically cause gallstones. Increased risk of gallstones can be seen with some causes of anemia such as sickle cell disease and

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- **Hypertension:** EPO increases systemic vascular resistance, possibly due to activation of erythropoietin receptors on vascular endothelial and smooth muscle cells. This can result in hypertensive encephalopathy and increased risk of **cardiovascular events** (eg, stroke, myocardial infarction).

To avoid morbidity, most studies recommend **cessation** of recombinant EPO once hemoglobin improves to **12-13 g/dL**; attempting to increase hemoglobin >13 g/dL increases the risk of adverse effects and death.

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(Choice C) The use of recombinant EPO does not usually increase bilirubin and does not typically cause gallstones. Increased risk of gallstones can be seen with some causes of anemia such as sickle cell disease and thalassemia.

(Choice D) Recombinant EPO stimulates erythrocytosis, which can rapidly consume iron stores (it does not cause iron overload). Therefore, iron levels should be monitored before and during treatment to ensure that iron deficiency does not occur.

Educational objective:
Patients with chronic kidney disease often develop normocytic anemia due to erythropoietin (EPO) deficiency. Treatment with recombinant EPO can dramatically improve tissue oxygen delivery and reduce mortality. However, prolonged or high-dose treatment can have serious side effects, most notably increased risk of hypertension and thromboembolism.

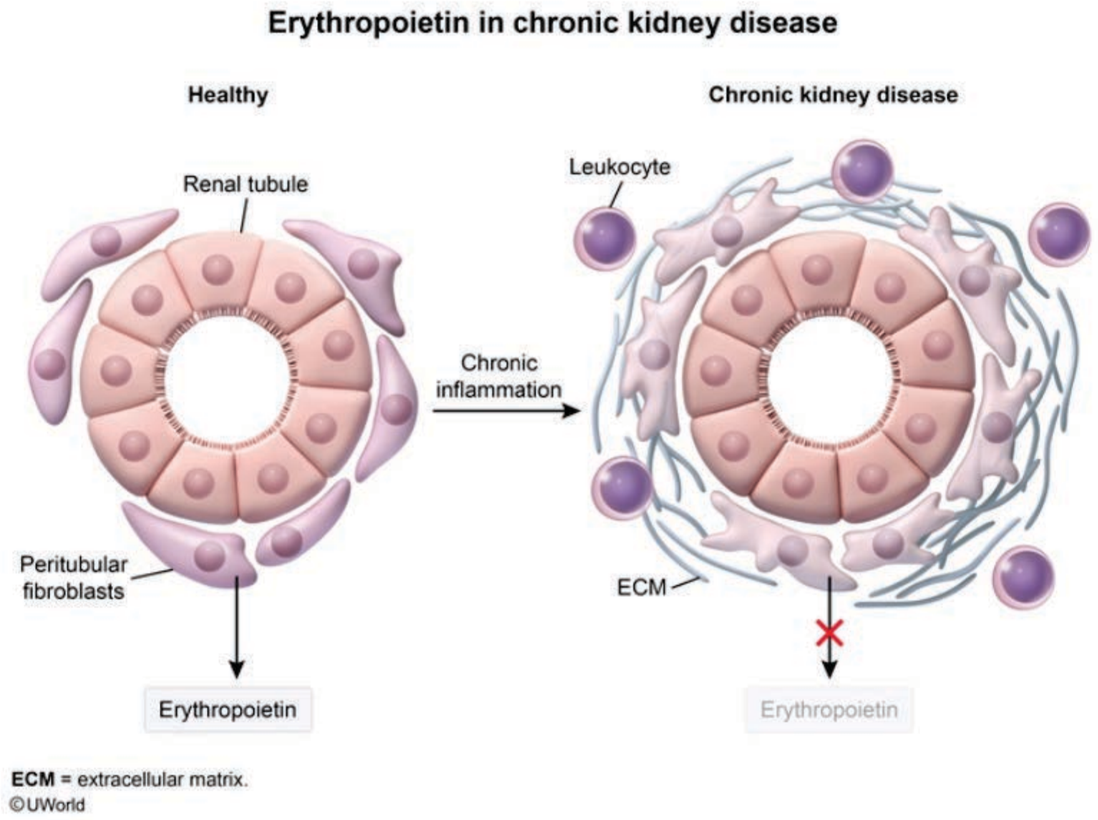
References

- Clinical use of erythropoietin in chronic kidney disease: outcomes and future prospects.

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C. Gallstone formation (4%)

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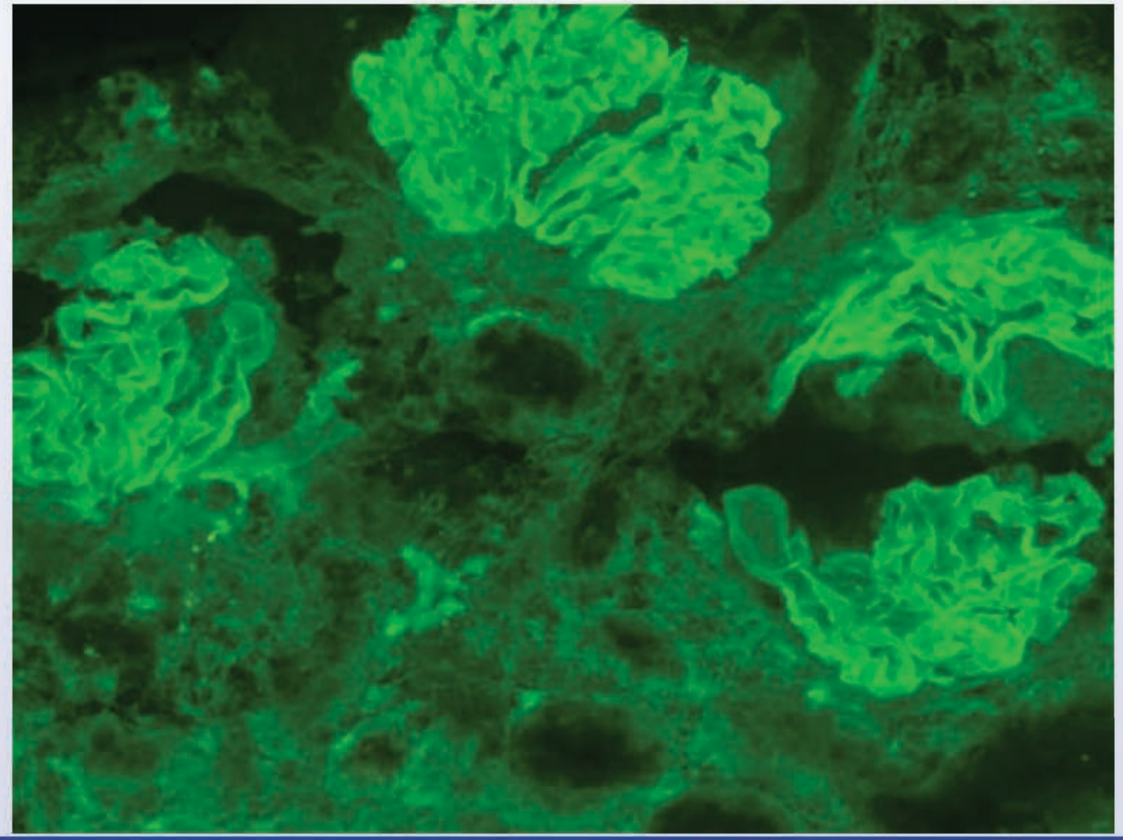
ECM = extracellular matrix.
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To avoid morbidity, most studies recommend **cessation** of recombinant EPO once hemoglobin improves to **12-13**

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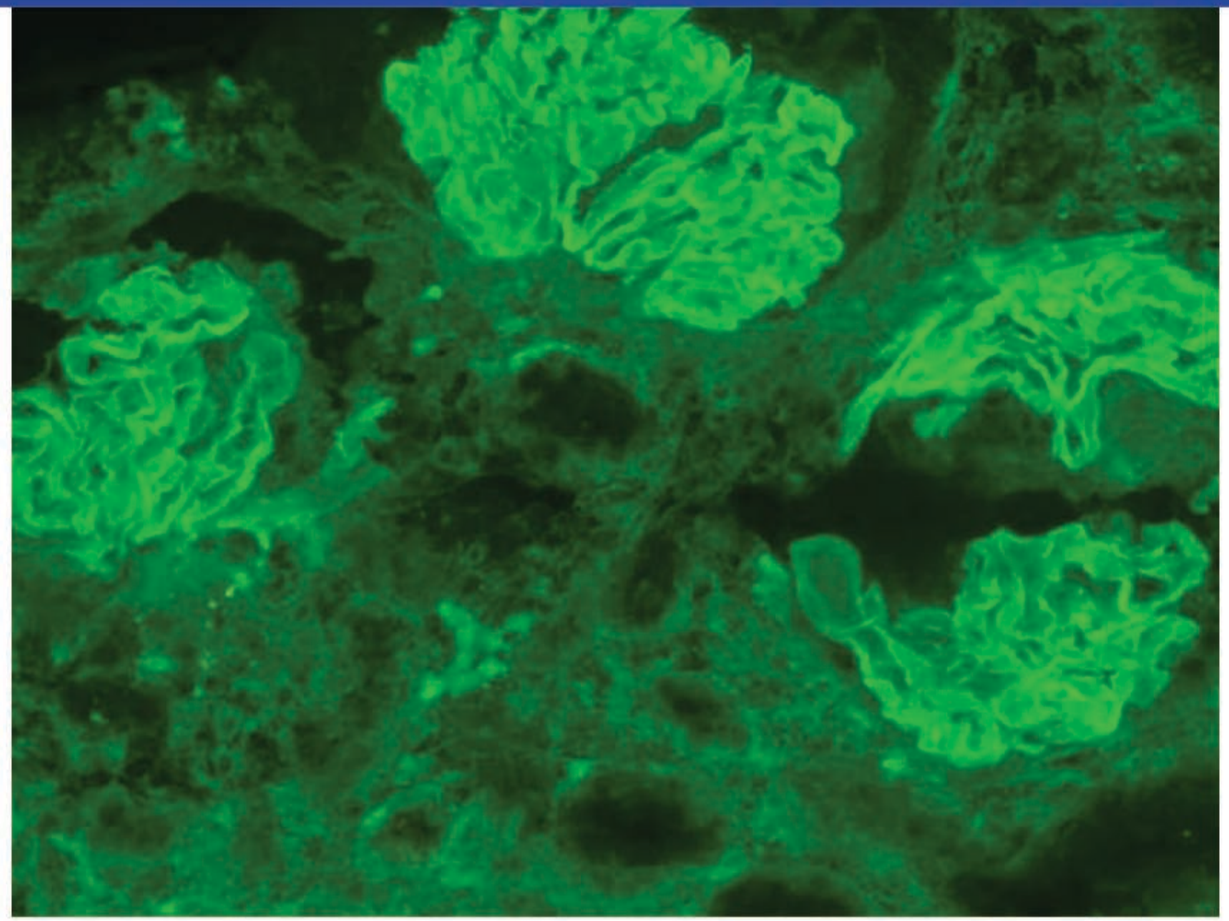
A 43-year-old man comes to the office due to shortness of breath and fatigue. Over the last 2 weeks, his fatigue has been so profound that he has "little energy, even to get out of bed." The patient has no chills but has experienced recent weight gain and ankle swelling. He has no prior medical conditions and takes no medications. Blood pressure is 168/94 mm Hg, and pulse is 95/min and regular. The patient has bilateral lower extremity pitting edema limited to the ankles. Urinalysis reveals 2+ protein, a white blood cell count of 5-7/hpf, and a red blood cell count of 75-100/hpf. The patient undergoes a kidney biopsy; immunofluorescent microscopy findings are shown in the image below.



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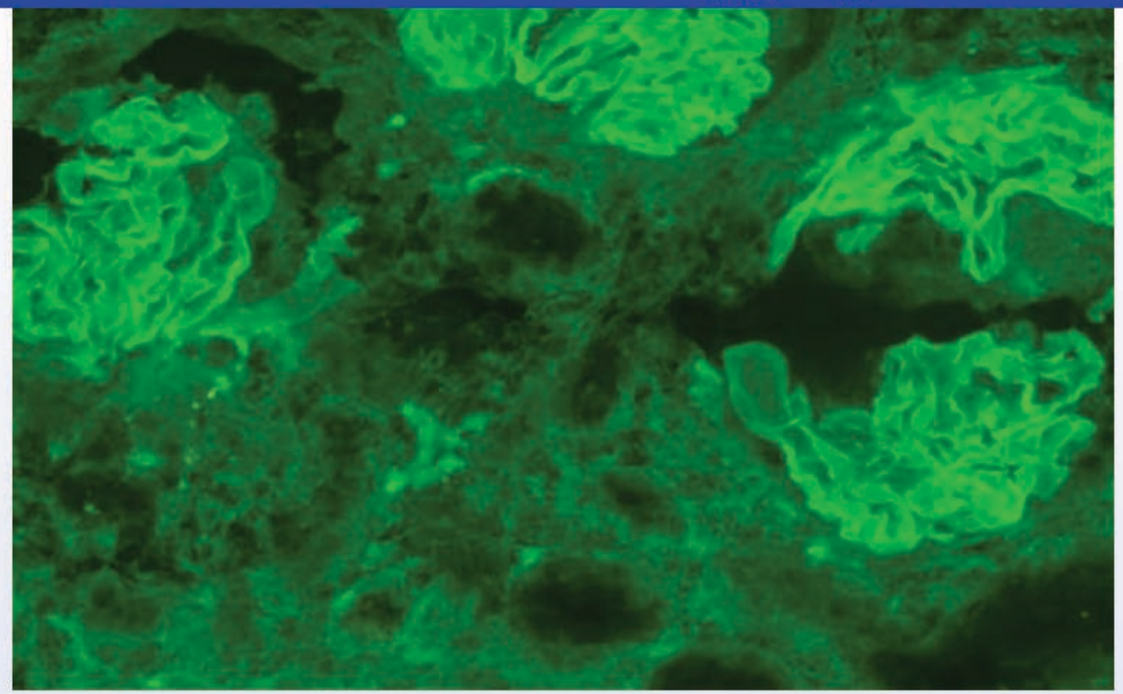
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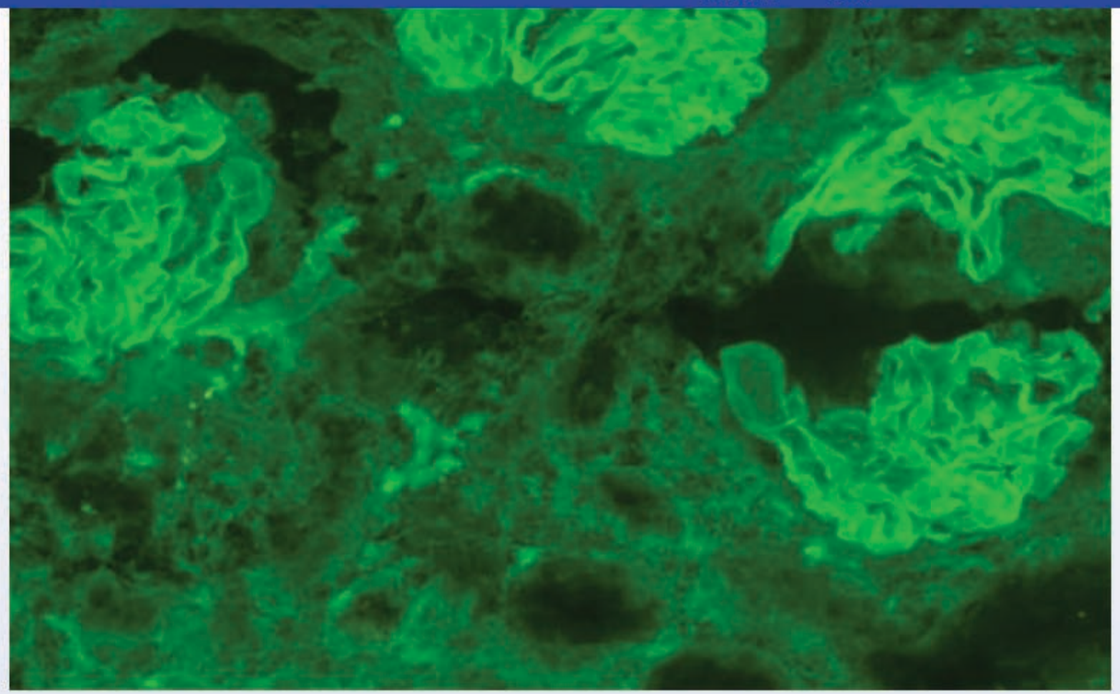


Which of the following would most likely be seen on light microscopy in this patient?

- A. Amyloid deposition
- B. Crescent formation
- C. Diffuse capillary wall thickening
- D. Nodular glomerulosclerosis
- E. Normal glomeruli

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Which of the following would most likely be seen on light microscopy in this patient?

- A. Amyloid deposition (15%)
- ✓ B. Crescent formation (42%)
- C. Diffuse capillary wall thickening (25%)
- D. Nodular glomerulosclerosis (12%)
- E. Normal glomeruli (2%)

Correct

42% Answered correctly

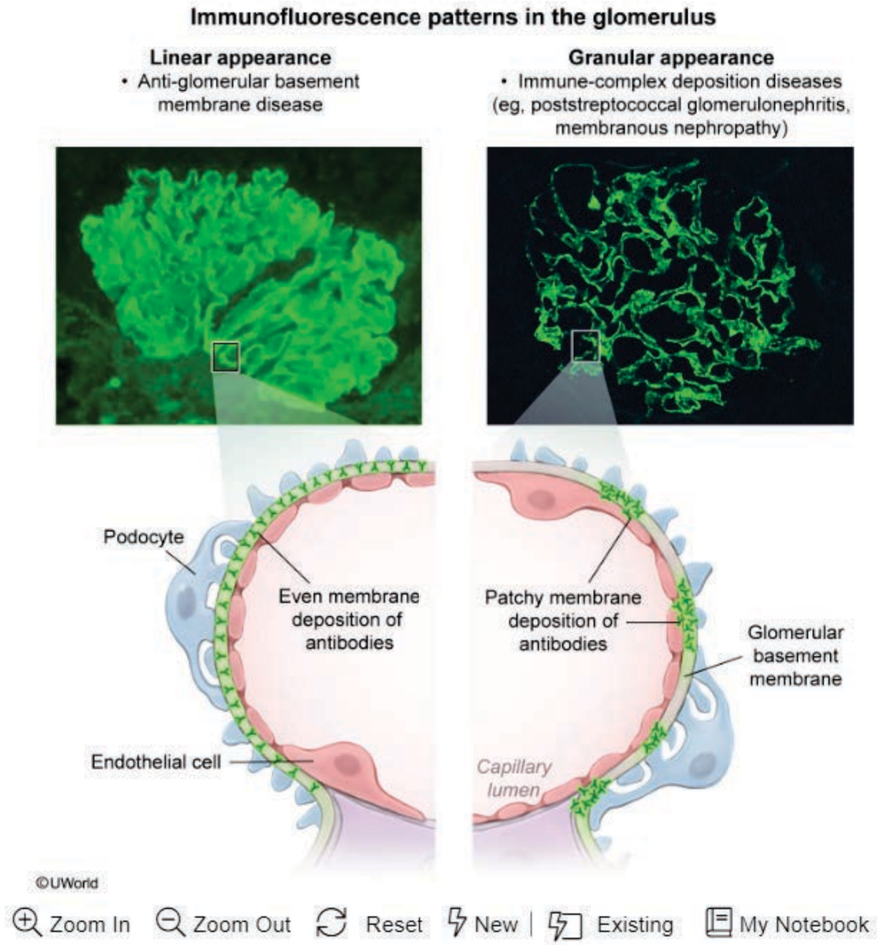
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E. Normal glomeruli (2%)

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This patient's hypertension, hematuria (with mild pyuria), and moderate proteinuria are indicative of nephritic syndrome. Immunofluorescence microscopy further demonstrates **linear deposits** (ie, ribbon-like) along the glomerular basement membrane (GBM), a finding characteristic of **anti-GBM disease**. In this condition, anti-GBM autoantibodies (usually **IgG**) develop against the alpha-3 chain of **type IV collagen** (a subunit found in high concentration in the GBM). Subsequent complement deposition (eg, **C3**) and leukocyte infiltration lead to rapidly progressive (crescentic) glomerulonephritis (RPGN).

RPGN is a syndrome of severe renal injury that manifests with acute-onset hematuria and decreased glomerular filtration (weight gain, edema). It can occur due to multiple diseases (eg, granulomatosis with polyangiitis, microscopic polyangiitis). The presence of glomerular crescents—composed of proliferating parietal cells, lymphocytes, macrophages, and fibrin—on light microscopy is diagnostic.

Anti-GBM antibodies also **cross-react** with pulmonary **alveolar** basement membranes, which are also enriched in the alpha-3 subchain, causing diffuse alveolar damage and hemorrhage. The combination of glomerulonephritis and pulmonary hemorrhage in patients with anti-GBM antibodies is known as **Goodpasture syndrome**.

(Choice A) Renal amyloidosis causes a nephrotic syndrome (ie, heavy proteinuria, hypoalbuminemia, hyperlipidemia, edema); significant hematuria is unexpected. Immunofluorescence microscopy is nonspecific and may show diffuse mesangial staining (rather than distinct, linear immune deposits on the GBM). On Congo red staining, amyloid deposits appear red-pink under light microscopy and have an apple-green birefringence under polarized light.

(Choice C) In membranous nephropathy, which causes a nephrotic syndrome, immunofluorescence demonstrates *granular deposits* of IgG and C3 along the GBM. Uniform, diffuse capillary wall thickening is seen on light microscopy.

(Choice D) Nodular glomerulosclerosis (Kimmelstiel-Wilson lesion) and mesangial expansion are seen on light microscopy in diabetic nephropathy, which presents as a nephrotic syndrome. There are no immune deposits on immunofluorescence.

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RPGN is a syndrome of severe renal injury that manifests with acute-onset hematuria and decreased glomerular filtration (weight gain, edema). It can occur due to multiple diseases (eg, granulomatosis with polyangiitis, microscopic polyangiitis). The presence of glomerular crescents—composed of proliferating parietal cells, lymphocytes, macrophages, and fibrin—on light microscopy is diagnostic.

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(Choice D) Nodular glomerulosclerosis (Kimmelstiel-Wilson lesion) and mesangial expansion are seen on light microscopy in diabetic nephropathy, which presents as a nephrotic syndrome. There are no immune deposits on immunofluorescence.

(Choice E) Normal glomeruli are found on light microscopy in minimal change disease, a condition that primarily affects children and presents as a nephrotic syndrome. There are no immune deposits on immunofluorescence.

Educational objective:
Anti-glomerular basement membrane (GBM) antibodies react with collagen type IV, causing rapidly progressive glomerulonephritis with glomerular crescent formation on light microscopy. Immunofluorescence demonstrating linear (ribbon-like) deposits of IgG and C3 along the GBM is characteristic.

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Pathologic findings in nephritic syndrome

	Cause of glomerular injury	Characteristic biopsy features
Poststreptococcal glomerulonephritis	Antibodies against streptococcal antigens that deposit in GBM	• IF: C3 granular staining along GBM • EM: subepithelial humps
Anti-GBM disease	Antibodies against type IV collagen in GBM	• LM: glomerular crescents • IF: linear staining (IgG) along GBM
Rapidly progressive glomerulonephritis	Severe immunologic injury (eg, anti-GBM antibodies, immune complex deposition)	• LM: glomerular crescents • IF: fibrin in crescents
IgA nephropathy	Deposition of IgA-containing complexes	• LM: mesangial hypercellularity • IF: IgA in mesangium
Alport syndrome	Defective type IV collagen in GBM	• EM: lamellated appearance of GBM

EM = electron microscopy; **GBM** = glomerular basement membrane; **IF** = immunofluorescence; **LM** = light microscopy.

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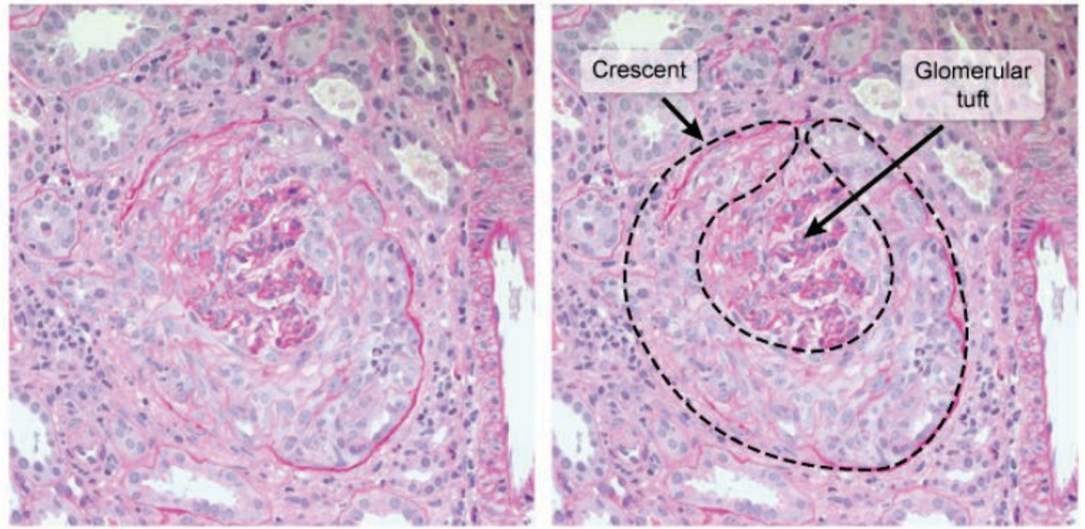
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(Choice D) Nodular glomerulosclerosis (Kimmelstiel-Wilson lesion) and mesangial expansion are seen on light

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Crescentic glomerulonephritis



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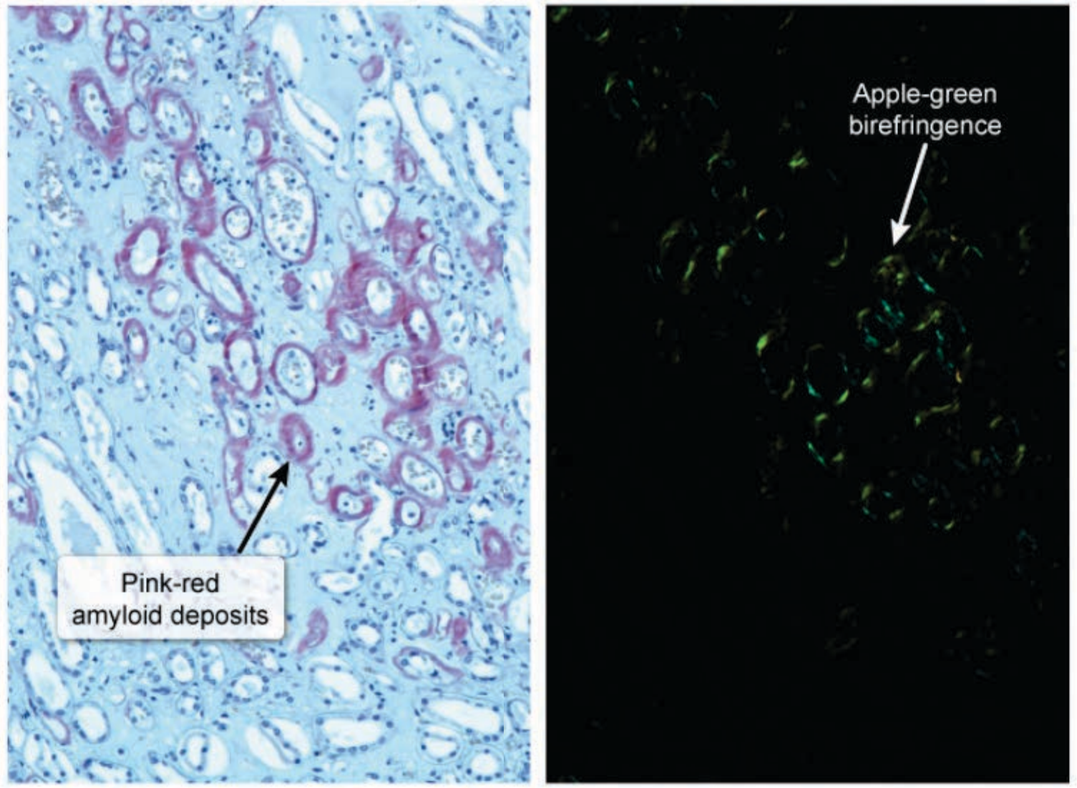
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(Choice D) Nodular glomerulosclerosis (Kimmelstiel-Wilson lesion) and mesangial expansion are seen on light

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Renal amyloidosis



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Congo red stain

Congo red stain under polarized light

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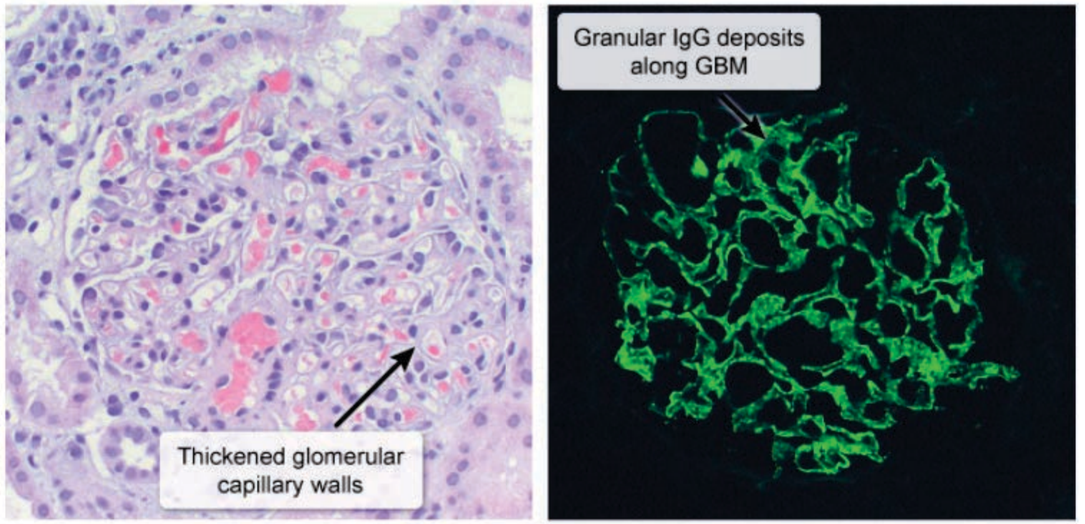
(Choice D) Nodular glomerulosclerosis (Kimmelstiel-Wilson lesion) and mesangial expansion are seen on light

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syndrome. Immunofluorescence microscopy further demonstrates **linear deposits** (ie, ribbon-like) along the

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Membranous nephropathy



Hematoxylin & eosin stain

Immunofluorescence

GBM = glomerular basement membrane.

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syndrome. Immunofluorescence microscopy further demonstrates **linear deposits** (ie, ribbon-like) along the

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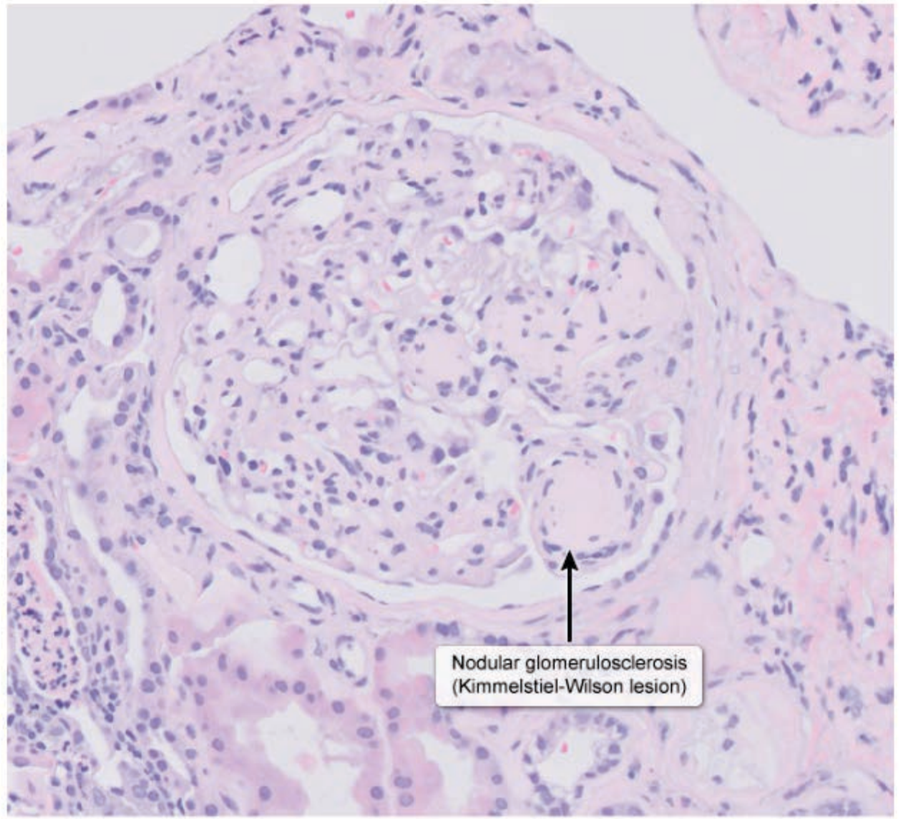
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immunofluorescence.

(Choice E) Normal glomeruli are found on light microscopy in minimal change disease, a condition that primarily

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Diabetic nephropathy



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A 54-year-old man comes to the physician due to blood in his urine and abdominal discomfort that occurred 2 days ago. He was moving potted plants around his porch when he started having pain in his abdomen. Afterward, he noticed blood in his urine but says it resolved the following day. He has a history of hypertension. The patient does not use tobacco, alcohol, or illicit drugs. Physical examination shows no abnormalities. CT scan of the abdomen with contrast is shown below.



Which of the following is the most likely diagnosis?

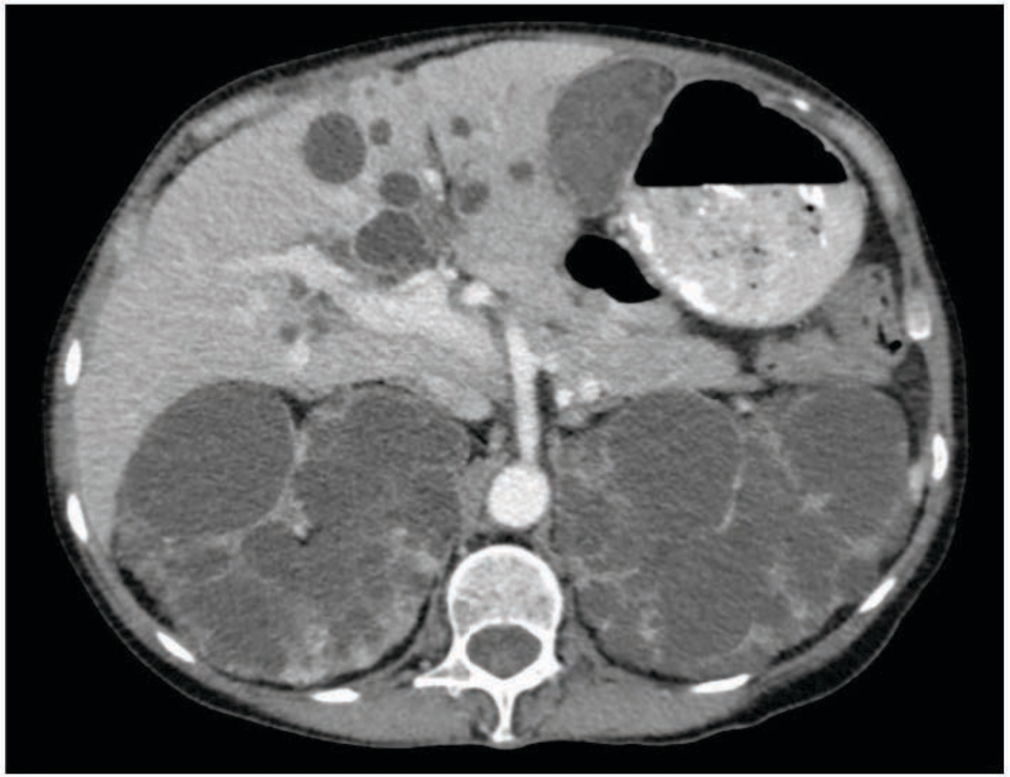
A. Glomerulonephritis

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A 54-year-old man comes to the physician due to blood in his urine and abdominal discomfort that occurred 2 days ago. He noticed that his urine was dark brown in color. He does not have any pain with urination. He has had abdominal discomfort in the left flank region. He has no history of recent illness. He has a history of hypertension and hyperlipidemia. He has had a 30-pack-year history of smoking. He drinks 2 beers per day. His father died of a myocardial infarction at the age of 60 years. His mother has hypertension. His temperature is 37°C (98.6°F), pulse is 80/min, and blood pressure is 130/80 mm Hg. Physical examination shows no abnormalities. Laboratory studies show:

Hemoglobin	14 g/dL
Leukocyte count	7,000/mm³
Platelet count	250,000/mm³
Urinalysis	
Blood	3+
Protein	Negative
Glucose	Negative
Leukocyte esterase	Negative
Nitrite	Negative
Microscopic examination	0–2 RBC/hpf

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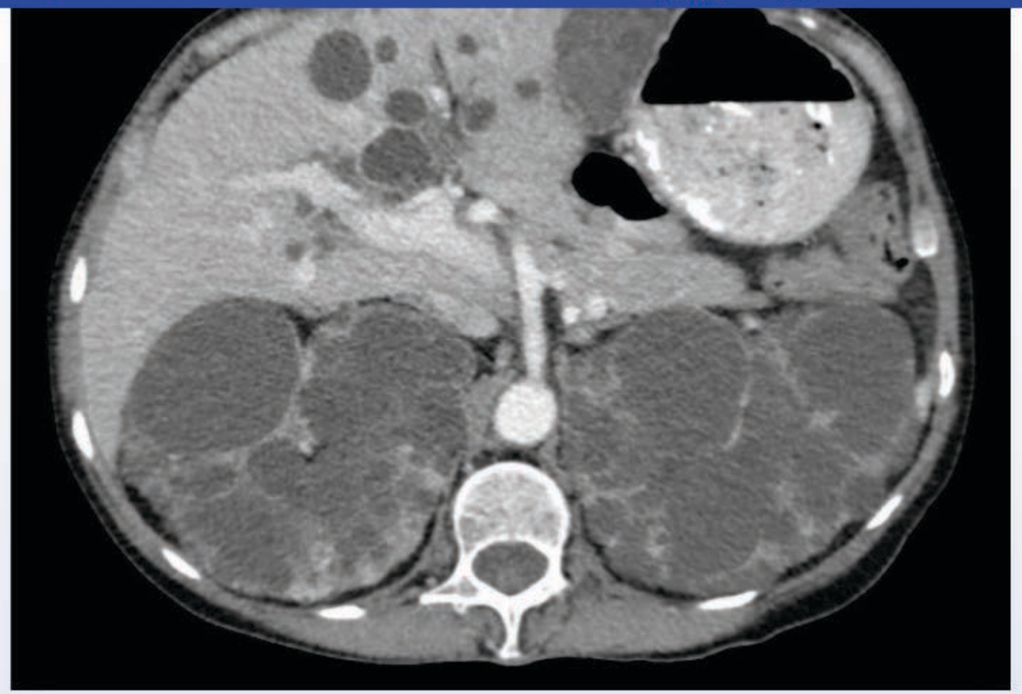


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Which of the following is the most likely diagnosis?

A. Glomerulonephritis

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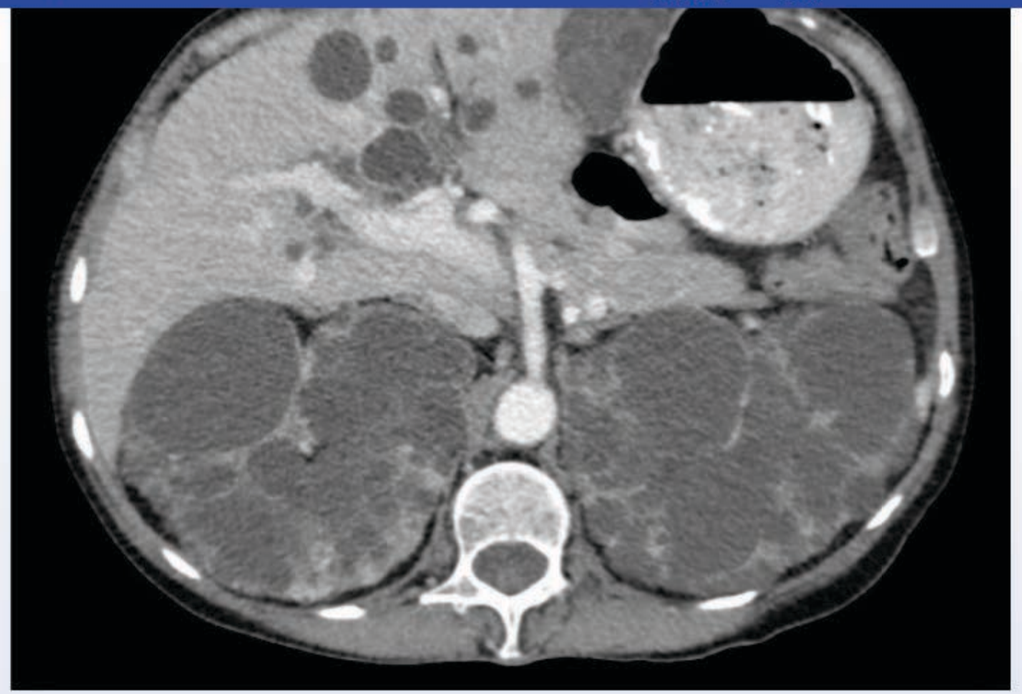


Which of the following is the most likely diagnosis?

- A. Glomerulonephritis
- B. Hydronephrosis
- C. Nephroblastoma
- D. Polycystic kidney disease
- E. Renal cell carcinoma

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Which of the following is the most likely diagnosis?

- A. Glomerulonephritis (1%)
- ✗ B. Hydronephrosis (5%)
- C. Nephroblastoma (1%)
- ✓ D. Polycystic kidney disease (81%)
- E. Renal cell carcinoma (10%)

Incorrect
Correct answer
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81%
Answered correctly

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Explanation

Autosomal dominant polycystic kidney disease	
Genetics	• Autosomal dominant mutation in *PKD1* or *PKD2*
Clinical features	• **Symptoms:** often asymptomatic; ± abdominal/flank pain • **Signs:** hypertension, hematuria, progressive renal failure
Imaging	• Multiple renal cysts (thin-walled, nonenhancing)
Extrarenal manifestations	• Liver cysts • Cerebral aneurysms

This patient with flank pain, hematuria, hypertension, and multiple renal and hepatic cysts on imaging (smooth, thin walls with nonenhancing cystic fluid) has **autosomal dominant polycystic kidney disease** (ADPKD). ADPKD is the most common hereditary cause of renal failure in **adults** and is caused by mutations in the polycystin genes (*PKD1*, *PKD2*) that result in progressive cystic enlargement of the kidneys.

Patients often remain asymptomatic until their fourth or fifth decade, when relentless enlargement of the cysts begins to impair renal function; **hypertension** is often the earliest clinical sign. Stretching of the renal capsule and dilation/rupture of the cysts can result in abdominal/flank pain; cyst rupture can also cause gross hematuria. Renal dysfunction worsens with age, and approximately 50% of adults progress to **end-stage renal disease** by age 70. Extrarenal manifestations include **liver cysts** and **intracranial aneurysms** that may rupture.

(Choice A) Glomerulonephritis can cause hematuria, hypertension, and renal failure but is not associated with cyst formation. Casts are typically visible on urinalysis.

(Choice B) Hydronephrosis can cause hematuria and pain, particularly if associated with an obstructing stone. However, dilation of the ureters and calyces would be expected on imaging.

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Extrarenal manifestations	• Liver cysts • Cerebral aneurysms

This patient with flank pain, hematuria, hypertension, and multiple renal and hepatic cysts on imaging (smooth, thin walls with nonenhancing cystic fluid) has **autosomal dominant polycystic kidney disease** (ADPKD). ADPKD is the most common hereditary cause of renal failure in **adults** and is caused by mutations in the polycystin genes (*PKD1*, *PKD2*) that result in progressive cystic enlargement of the kidneys.

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(Choice C) Nephroblastoma (Wilms tumor) is the most common pediatric renal malignancy but is rare in adults. It typically presents with a painful abdominal mass, hematuria, and hypertension. CT scan demonstrates a solid, heterogenous renal mass with patchy enhancement.

(Choice E) Renal cell carcinoma is the most common renal malignancy in adults and often presents with hematuria, hypertension, and flank pain. However, imaging typically demonstrates solitary renal mass with areas of contrast enhancement and focal necrosis; bilateral cystic changes would be unexpected.

Educational objective:
Autosomal dominant (adult) polycystic kidney disease is caused by mutations in the polycystin genes (*PKD1*, *PKD2*), which result in cystic enlargement of the kidneys and progressive renal dysfunction. Clinical features

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walls with nonenhancing cystic fluid) has **autosomal dominant polycystic kidney disease** (ADPKD). ADPKD is the most common hereditary cause of renal failure in **adults** and is caused by mutations in the polycystin genes (*PKD1*, *PKD2*) that result in progressive cystic enlargement of the kidneys.

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Educational objective:
Autosomal dominant (adult) polycystic kidney disease is caused by mutations in the polycystin genes (*PKD1*, *PKD2*), which result in cystic enlargement of the kidneys and progressive renal dysfunction. Clinical features include hypertension, abdominal/flank pain, and gross hematuria; extrarenal manifestations include liver cysts and intracranial aneurysms.

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Correct answer
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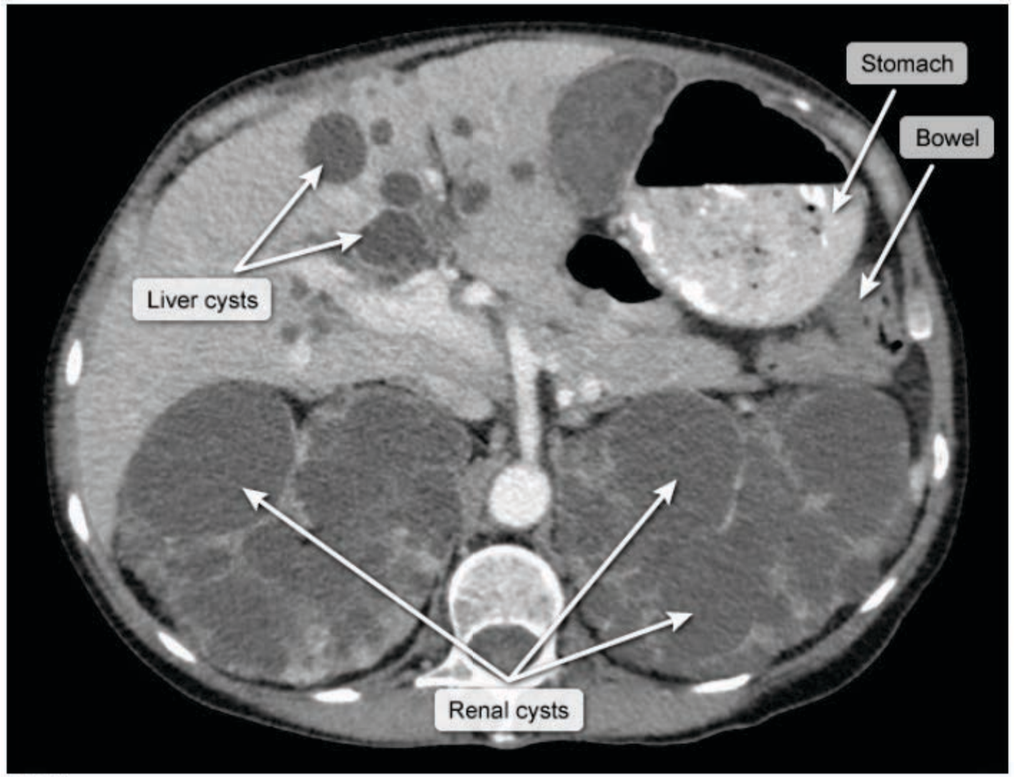
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Autosomal dominant polycystic kidney disease



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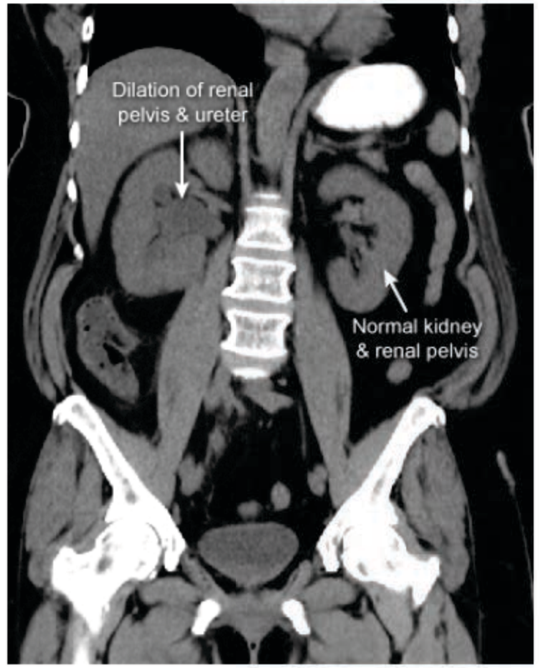
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features	• **Signs:** hypertension, hematuria, progressive renal failure

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Hydronephrosis



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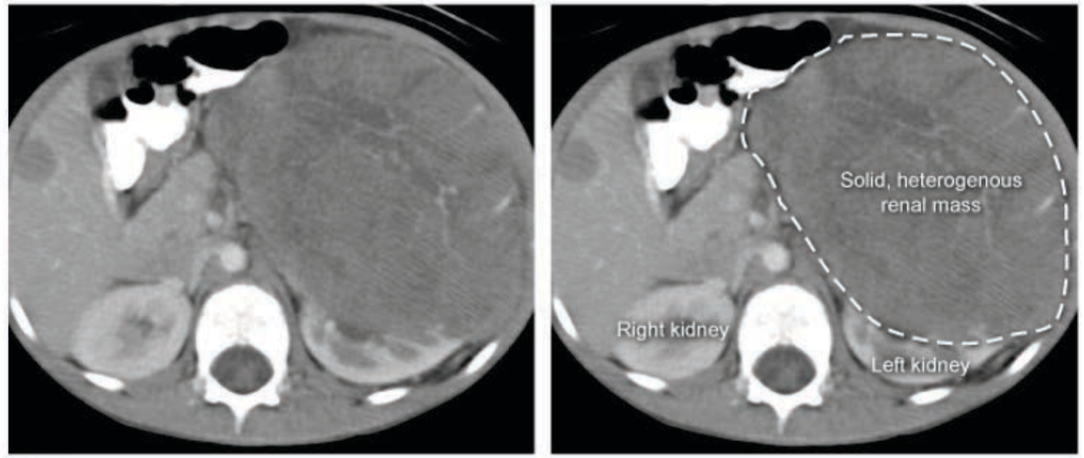
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features	• **Signs:** hypertension, hematuria, progressive renal failure

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Wilms tumor (nephroblastoma)



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hematuria, hypertension, and flank pain. However, imaging typically demonstrates solitary renal mass with areas of contrast enhancement and focal necrosis; bilateral cystic changes would be unexpected.

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A 58-year-old man comes to the office due to fatigue, decreased appetite, muscle cramps, and nausea. The patient has chronic kidney disease resulting from primary focal segmental glomerulosclerosis. His current medications include a vitamin D supplement. While his blood pressure is being obtained, the patient develops carpal spasm. Bilateral lower extremity pedal edema is noted. Laboratory evaluation shows a blood urea nitrogen level of 120 mg/dL, serum creatinine level of 10 mg/dL, and serum calcium level of 6 mg/dL. Which of the following is most likely contributing to this patient's carpal spasm?

- A. Hyperphosphatemia
- B. Hypoparathyroidism
- C. Low albumin level
- D. Low fibroblast growth factor 23 level
- E. Vitamin D toxicity

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A 58-year-old man comes to the office due to fatigue, decreased appetite, muscle cramps, and nausea. The patient has chronic kidney disease resulting from primary focal segmental glomerulosclerosis. His current medications include a vitamin D supplement. While his blood pressure is being obtained, the patient develops carpal spasm. Bilateral lower extremity pedal edema is noted. Laboratory evaluation shows a blood urea nitrogen level of 120 mg/dL, serum creatinine level of 10 mg/dL, and serum calcium level of 6 mg/dL. Which of the following is most likely contributing to this patient's carpal spasm?

- ✓ A. Hyperphosphatemia (64%)
- ✗ B. Hypoparathyroidism (21%)
- C. Low albumin level (5%)
- D. Low fibroblast growth factor 23 level (2%)
- E. Vitamin D toxicity (5%)

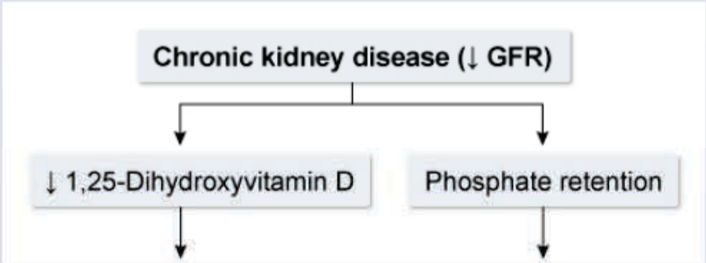
Incorrect
Correct answer
A

64%
Answered correctly

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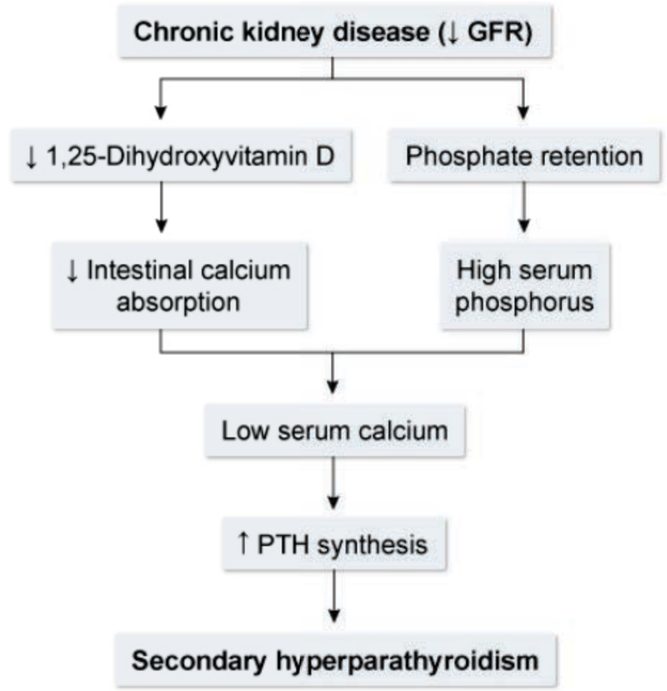
Explanation



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E. Vitamin D toxicity (5%)

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GFR = glomerular filtration rate; **PTH** = parathyroid hormone.

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This patient with **chronic kidney disease** (CKD) has developed carpal spasm secondary to hypocalcemia. In CKD, reduced filtration and excretion of phosphorus causes **hyperphosphatemia**, which induces **hypocalcemia** through the following mechanisms:

- Released phosphate binds to free calcium and precipitates in soft tissues (which, over the long term, can lead to vascular calcification and stiffness)
- Increased serum phosphate triggers the release of fibroblast growth factor 23 from bone, which acts to lower phosphate levels in part by inhibiting renal expression of 1-alpha hydroxylase. This reduces production of 1,25-dihydroxyvitamin D (calcitriol), leading to reduced intestinal calcium absorption

Hypocalcemia is also worsened by the progressive loss of functioning renal tissue in CKD, which further reduces calcitriol synthesis.

Hypocalcemia can cause alterations in cellular membrane potentials and **neuromuscular excitability**. Manifestations include muscle cramps, Chvostek (**facial twitching** elicited by tapping on the facial nerve) and Trousseau (**carpal spasm** triggered by inflation of a blood pressure cuff around the arm) signs, hyperreflexia, QTc prolongation, and seizures.

(Choice B) The hypocalcemia and hyperphosphatemia that occur in patients with CKD stimulate secretion of parathyroid hormone (ie, secondary hyperparathyroidism). By contrast, hypoparathyroidism is usually due to autoimmune disease or iatrogenic injury during thyroid surgery and is not a common finding in CKD.

(Choice C) Serum calcium is composed of an ionized free calcium fraction and a protein-bound (largely to albumin) fraction; only ionized calcium is metabolically active. Hypoalbuminemia can occur in patients with nephrotic syndrome (eg, this patient with focal segmental glomerulosclerosis). However, although hypoalbuminemia lowers the bound fraction (and therefore total serum calcium), ionized calcium remains normal, and patients do not experience hypocalcemic symptoms.

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(Choice D) Fibroblast growth factor 23 levels are usually low in patients with normal phosphate metabolism but are increased in patients with renal failure in response to hyperphosphatemia.

(Choice E) Vitamin D toxicity can occur in food faddists, patients with mental illness, and those inadvertently treated with excessive doses of vitamin D. However, this causes hypercalcemia, not hypocalcemia.

Educational objective:
In chronic kidney disease, reduced excretion of phosphate can cause hyperphosphatemia. This induces hypocalcemia directly by binding free calcium and depositing in tissues, and indirectly by triggering fibroblast growth factor 23 secretion (decreases calcitriol production and intestinal calcium absorption). The resulting hypocalcemia can manifest as neuromuscular excitability (eg, carpal spasm).

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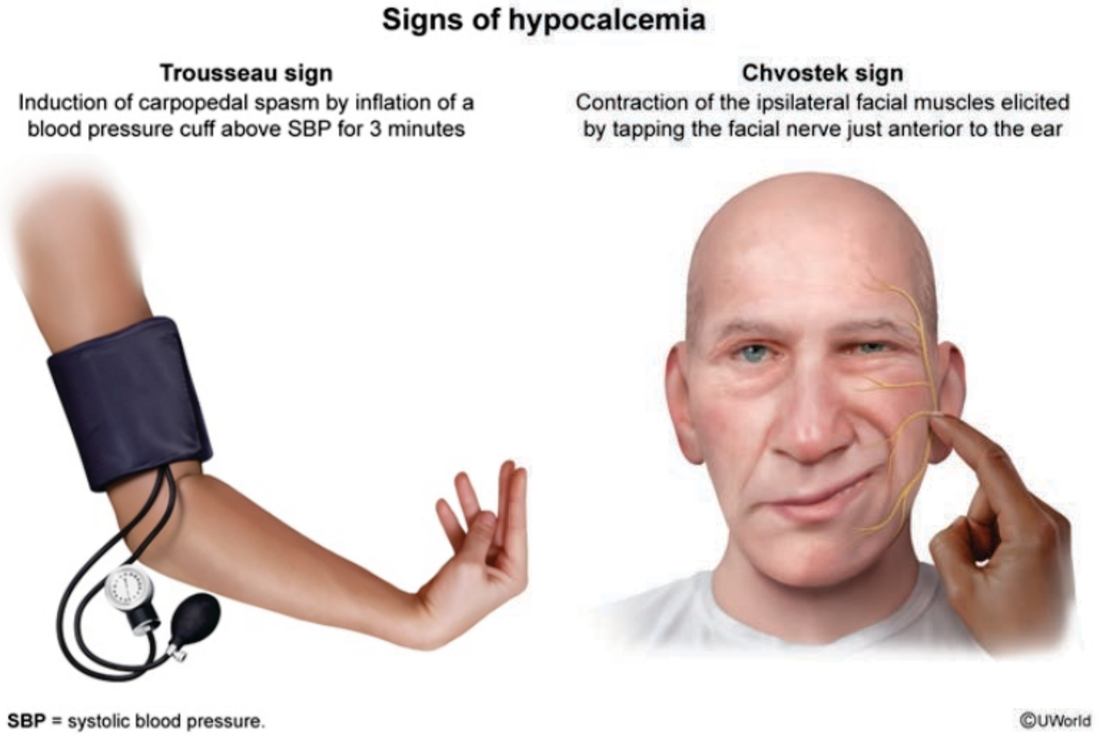
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Researchers are studying the mechanisms that lead to acute kidney injury in septic shock. In an experiment, the renal perfusion pressure of laboratory mice is reduced to assess changes in renal tubular function and morphology. Perfusion pressure is decreased until renal tubular dysfunction occurs due to sublethal cellular ischemia; recovery of function is achieved within several hours of reperfusion. Which of the following is most likely the earliest change to occur within the renal tubules during the ischemic period?

- A. Activation of cytoplasmic caspases
- B. Damage to the tubular basement membrane
- C. Loss of epithelial cell polarity
- D. Necrosis and sloughing of epithelial cells

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- A. Activation of cytoplasmic caspases (16%)
- ✗ B. Damage to the tubular basement membrane (18%)
- ✓ C. Loss of epithelial cell polarity (49%)
- D. Necrosis and sloughing of epithelial cells (15%)

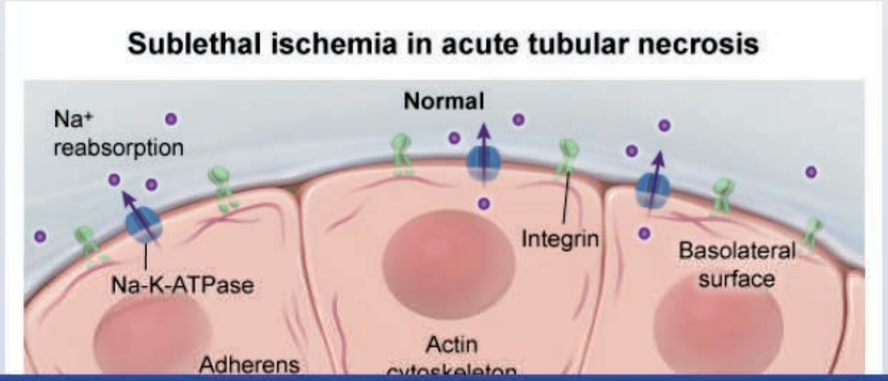
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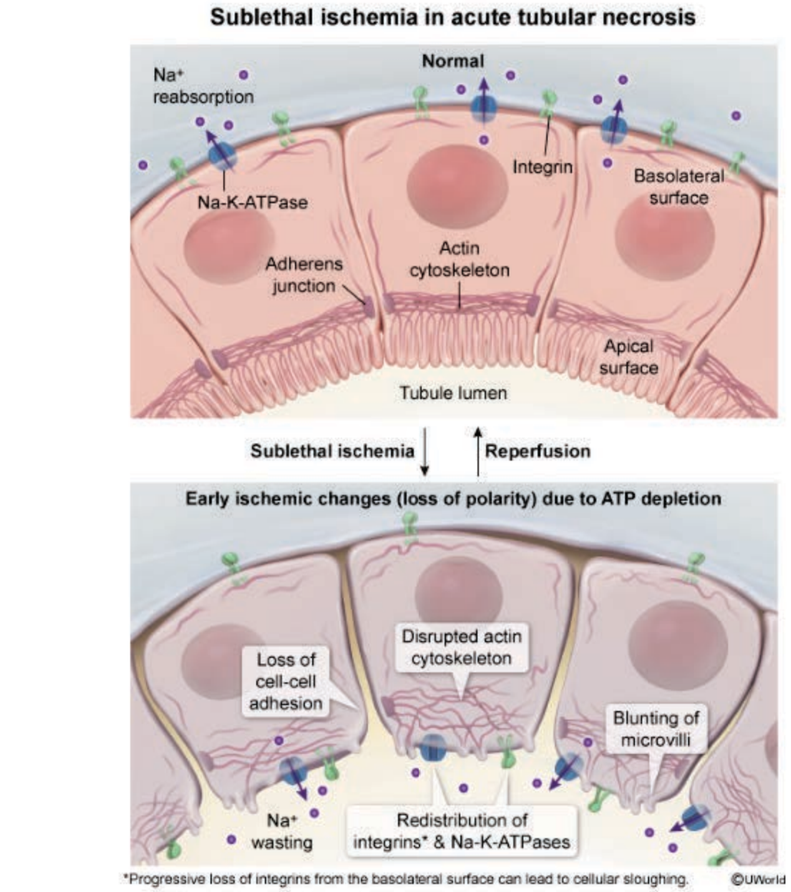
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Explanation



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The mice in this experimental study are observed to have rapidly reversible renal tubular dysfunction after exposure to sublethal ischemia, which is consistent with **acute tubular necrosis** (ATN). **Loss of epithelial cell polarity** occurs early in ATN due to alterations in the actin cytoskeleton. The actin cytoskeleton is very sensitive to depletion of ATP; therefore, ischemia causes rapid **cytoskeletal disruption**, resulting in:

- **Blunting of apical microvilli**, which reduces the surface area available for solute transport
- **Loss of cell-cell adhesion** (eg, tight junctions), which causes back leakage of tubular fluid into the interstitium
- **Redistribution of integrins** from the basolateral to apical membrane, which promotes cell detachment, tubular obstruction, and cast formation (by binding together detached epithelial cells)
- Redistribution of **Na-K-ATPases** from the basolateral membrane to the apical membrane, which disrupts the concentration gradient necessary for sodium reabsorption

Impaired sodium reabsorption results in sodium wasting and increases its distal delivery to the macula densa. The inappropriate juxtaglomerular feedback causes afferent arteriole constriction, which further worsens renal ischemia.

Prolonged renal ischemia eventually leads to necrosis, further sloughing of tubular epithelial cells, and tubular obstruction; if severe enough, this can damage the basement membrane and cause tubular rupture **(Choices B and D)**. Restoration of perfusion to cells exposed to sublethal injury allows for cellular polarity normalization and recovery of renal function.

(Choice A) Cellular apoptosis is driven by activation of cytoplasmic caspases in response to increased mitochondrial permeability. However, this occurs following prolonged, lethal ischemia rather than the short period of sublethal ischemia in this study.

Educational objective:
Loss of epithelial cell polarity is an early change that occurs in renal tubular cells in response to ischemia (ie, acute

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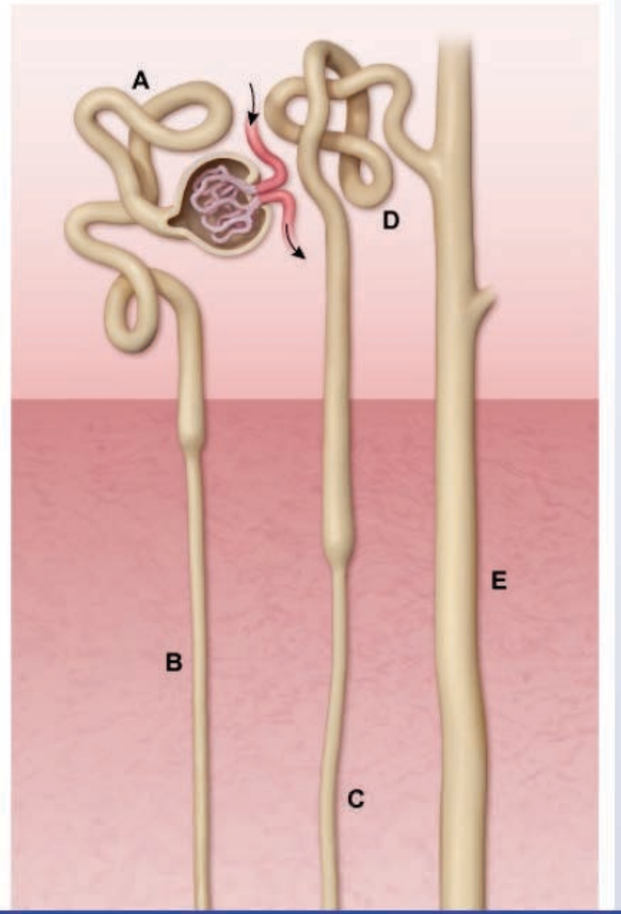
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Educational objective:
Loss of epithelial cell polarity is an early change that occurs in renal tubular cells in response to ischemia (ie, acute tubular necrosis). Depletion of ATP causes rapid cytoskeletal disruption; this leads to a loss of cell-cell adhesion and causes redistribution of integrins and Na-K-ATPases from the basolateral membrane to the apical membrane.

References

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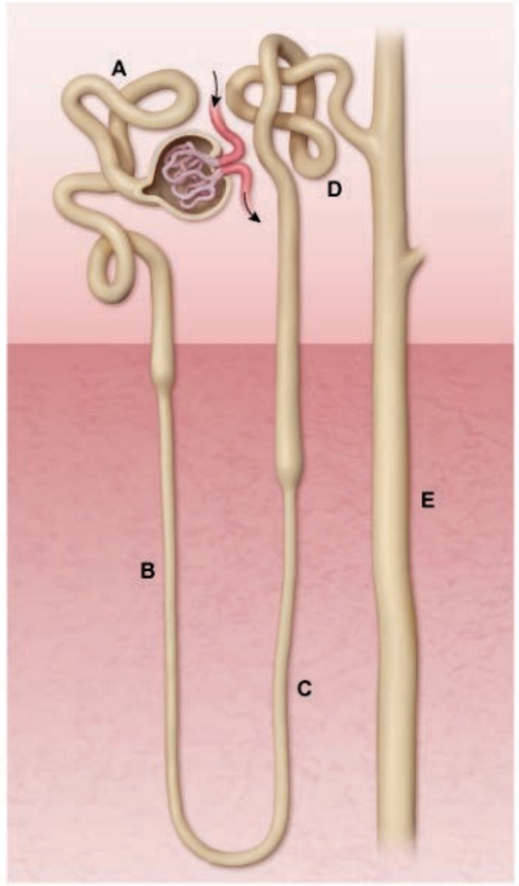
Renal physiologists are studying how hydration status affects the mechanisms of urine concentration and dilution in humans. To do this, they developed a technique in experimental animals that permits sampling of tubular fluid in different parts of the nephron. A tubular fluid sample with an osmolarity of 110 mOsm/L is obtained from a healthy animal after 12 hours of water deprivation. Assuming the physiology of this animal mirrors human physiology, which of the following sites along the nephron was most likely sampled?



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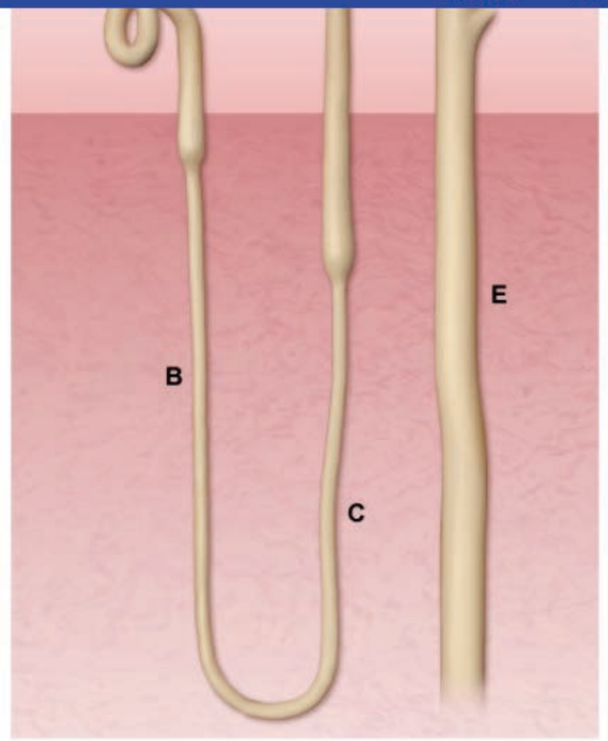
Renal physiologists are studying how hydration status affects the mechanisms of urine concentration and dilution in hum diffe anim whic

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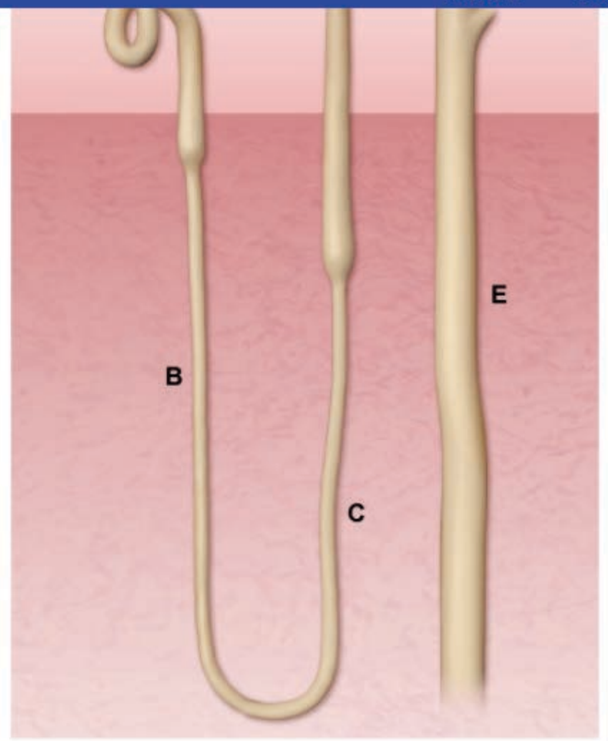
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- A. A
- B. B
- C. C
- D. D
- E. E

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- A. A (17%)
- ✗ B. B (9%)
- C. C (10%)
- ✓ D. D (45%)
- E. E (16%)

Incorrect
Correct answer
D

45%
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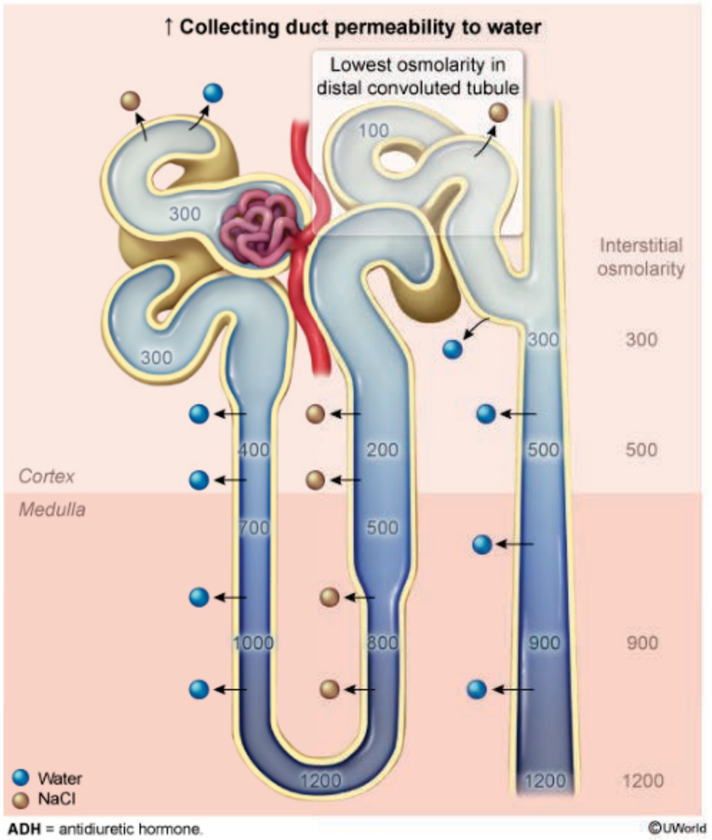
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F. F (16%)

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Tubular fluid osmolarity in the setting of high ADH



ADH = antidiuretic hormone.

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Water deprivation results in **antidiuretic hormone (ADH)** release from the posterior pituitary gland. This hormone stimulates V2 receptors on principal cells in the renal collecting ducts, causing translocation of aquaporin 2 channels into the apical cell membrane. Aquaporin 2 is a water channel that spans the luminal membrane, enhancing the water permeability of the principal cells. In the presence of **high ADH**, the tubular fluid osmolarity follows this pattern:

1. In the proximal tubule, water is reabsorbed along with electrolytes. The tubular fluid in this segment remains isotonic with plasma (300 mOsm/L) whether the final urine is concentrated or diluted **(Choice A)**.
2. In the descending limb of the loop of Henle, free water is drawn out of the tubules into the renal interstitium and the tubular fluid becomes hypertonic (> 300 mOsm/L, typically reaching 1200 mOsm/L when ADH levels are high) **(Choice B)**.
3. The thick and thin ascending limbs of the loop of Henle are the primary region of urine dilution. These regions are impermeable to water; electrolytes such as NaCl are passively reabsorbed in the thin ascending limb **(Choice C)** and actively reabsorbed in the thick ascending limb. The tubular fluid becomes increasing hypotonic (< 300 mOsm/L) within this region.
4. The **distal convoluted tubule** is relatively impermeable to water, so the tubular fluid remains hypotonic. Reabsorption of solutes continues to occur; thus, fluid in the distal tubules is the **most dilute** (lowest osmolarity, approaching 100 mOsm/L).
5. In the presence of ADH, the collecting duct is highly permeable to water. Water leaves the tubular fluid driven by the high osmolarity of the medullary interstitium, and **hypertonic urine** is formed (up to 1200 mOsm/L). The collecting duct system is the primary region of urine concentration through the mechanism of ADH-mediated water absorption.

(Choice E) In contrast, when ADH levels are low, the collecting duct remains impermeable to water. Thus, tubular

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(Choice E) In contrast, when ADH levels are low, the collecting duct remains impermeable to water. Thus, tubular fluid in this segment can become as hypotonic as 50 mOsm/L while solutes continue to be removed. However, in this case ADH levels are high, so the distal convoluted tubule will be the region of lowest osmolality.

Educational objective:
Dehydration stimulates ADH secretion. ADH acts on the collecting ducts, increasing their permeability to water. Thus, in the presence of ADH, the collecting ducts contain the most concentrated fluid in the nephron, while the distal convoluted tubule contains the most dilute fluid.

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channels into the apical cell membrane. Aquaporin 2 is a water channel that spans the luminal membrane,

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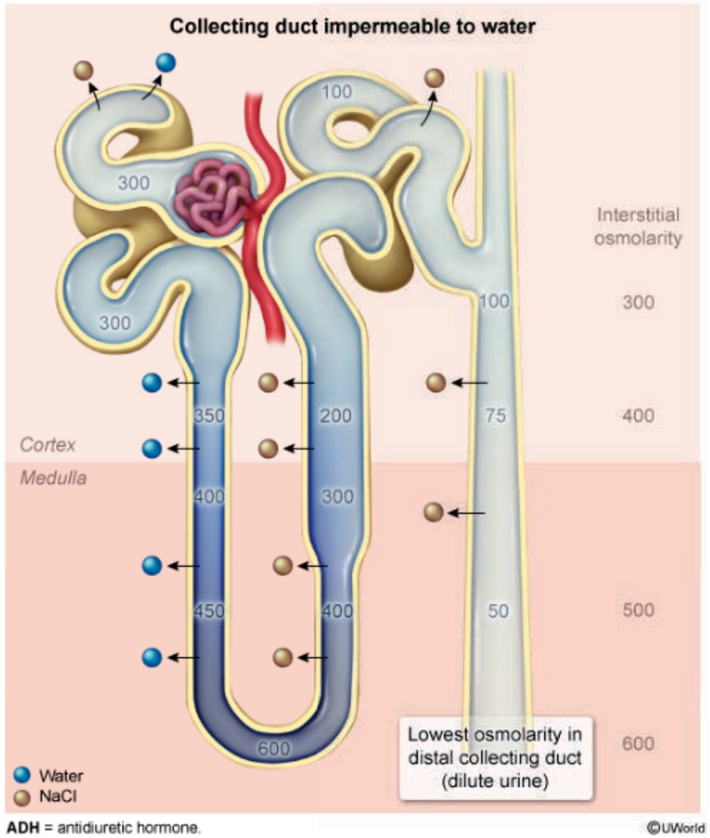
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Educational objective:

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Tubular fluid osmolarity in the setting of low ADH



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A 24-year-old woman comes to the office for the evaluation of joint pain, fatigue, edema, and weight gain for the past four weeks. She has no previous medical conditions except for recurrent oral ulcers. The patient takes no medications and does not use tobacco, alcohol, or illicit drugs. Blood pressure is 130/80 mm Hg and pulse is 80/min. Examination shows oral mucosal ulcers, facial puffiness, and 3+ peripheral edema. Swelling, erythema, and tenderness are noted over the bilateral metacarpophalangeal and proximal interphalangeal joints. Cardiopulmonary examination reveals no abnormalities. Twenty-four-hour urine protein excretion is 4.5 g. Serum antinuclear antibodies are present. Kidney biopsy shows glomerular capillary wall thickening with no increase in cellularity. When the sample is stained with methenamine silver, irregular spikes protruding from the glomerular basement membrane are seen. This patient most likely has which of the following conditions?

- A. Antiglomerular basement membrane disease
- B. Antineutrophil cytoplasmic antibody–associated glomerulonephritis
- C. Diffuse proliferative nephritis
- D. Focal segmental glomerulosclerosis
- E. Membranoproliferative glomerulonephritis
- F. Membranous nephropathy
- G. Postinfectious glomerulonephritis

Submit

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- A. Antiglomerular basement membrane disease (4%)
- ✗ B. Antineutrophil cytoplasmic antibody–associated glomerulonephritis (9%)
- C. Diffuse proliferative nephritis (8%)
- D. Focal segmental glomerulosclerosis (4%)
- E. Membranoproliferative glomerulonephritis (13%)
- ✓ F. Membranous nephropathy (58%)
- G. Postinfectious glomerulonephritis (1%)

Incorrect
Correct answer
F

58%
Answered correctly

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Explanation

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This patient has **nephrotic syndrome** (ie, generalized edema, marked proteinuria). In conjunction with the characteristic biopsy findings, this presentation suggests **membranous nephropathy** (MN). MN is caused by immune-complex deposition in the subepithelial portion of the glomerular capillary wall. Light microscopy shows **diffuse thickening** of the glomerular basement membrane (GBM) without an increase in glomerular cellularity. Immunofluorescence reveals granular deposits of IgG and C3 along the GBM. Electron microscopy demonstrates irregular, electron-dense immune deposits located between the GBM and epithelial cells. Protrusion of the GBM through the deposits resemble **spikes and domes** when stained with a silver stain.

MN is a common cause of nephrotic syndrome in adults. Most cases are idiopathic, with the remainder due to chronic infection (eg, viral hepatitis, syphilis), solid tumors (eg, lung, colon), or **systemic lupus erythematosus** (SLE). This patient with inflammatory arthritis, oral ulcers, and antinuclear antibodies likely has MN secondary to SLE (with anti–double-stranded DNA immune-complex deposition).

(Choices A and B) Anti-GBM disease (ie, Goodpasture disease) and antineutrophil cytoplasmic antibody–associated glomerulonephritis (eg, granulomatosis with polyangiitis) cause rapidly progressive crescentic disease, characterized by glomerular hypercellularity with crescent formation (composed of fibrin and proliferating cells). These diseases cause nephritic syndrome (eg, hematuria, red blood cell casts), not isolated proteinuria.

(Choice C) Diffuse proliferative nephritis, another common renal manifestation of SLE, is characterized by proliferation of lymphocytes and endothelial cells within the capillary loops. Diffuse "wire-loop" deposits are often seen.

(Choice D) Focal segmental glomerulosclerosis also causes nephrotic syndrome but is characterized by sclerosis in some glomeruli (focal) affecting only a portion (segmental) of the glomerulus. It is commonly associated with drug use (eg, heroin) and viruses (eg, HIV).

(Choice E) Membranoproliferative glomerulonephritis is often associated with hepatitis B or C. It is characterized by thickening of the GBM, but unlike MN, large hypercellular glomeruli are also seen.

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(Choice E) Membranoproliferative glomerulonephritis is often associated with hepatitis B or C. It is characterized by thickening of the GBM, but, unlike MN, large hypercellular glomeruli are also seen.

(Choice G) Postinfectious glomerulonephritis occurs more commonly in children and causes a nephritic (not nephrotic) syndrome, typically two to four weeks after a group A streptococcal infection. Light microscopy demonstrates enlarged, diffusely hypercellular glomeruli.

Educational objective:
Membranous nephropathy is a common cause of nephrotic syndrome in adults and can occur in association with solid malignancy, viral hepatitis, and systemic lupus erythematosus. Immune-complex deposition in the subepithelial portion of the glomerular capillary wall causes diffuse thickening of the glomerular basement membrane (without increased cellularity); these glomeruli have a "spike and dome" appearance when stained with a silver stain.

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This patient has **nephrotic syndrome** (ie, generalized edema, marked proteinuria). In conjunction with the

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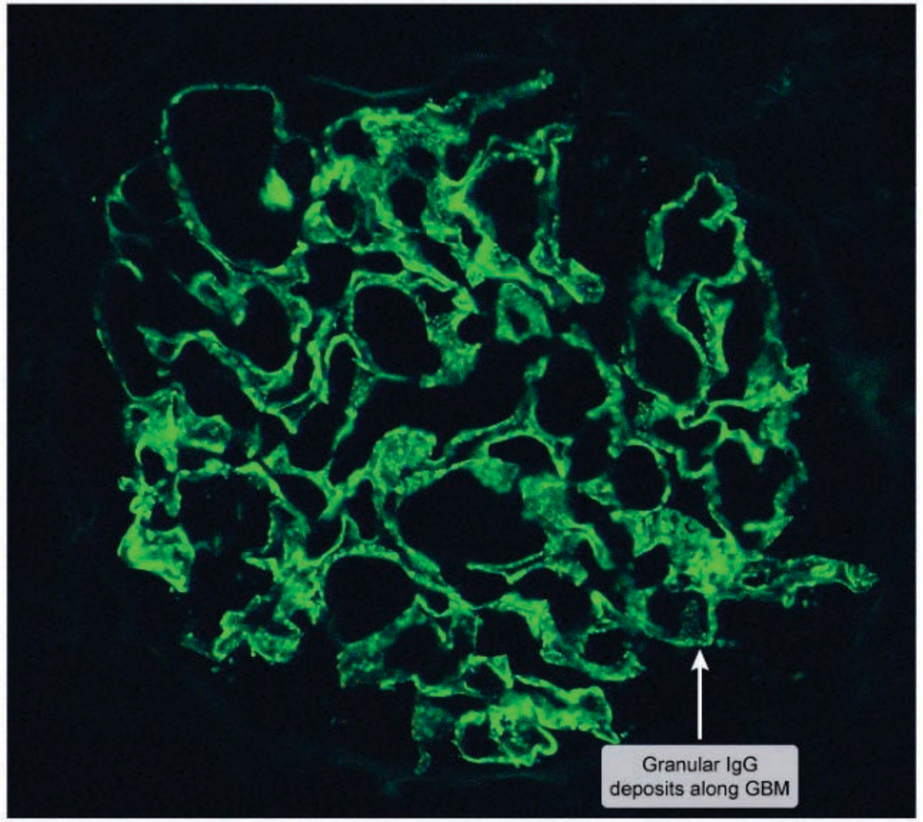
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(Choice G) Postinfectious glomerulonephritis occurs more commonly in children and causes a nephritic (not

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Membranous nephropathy



GBM = glomerular basement membrane. ©UWorld

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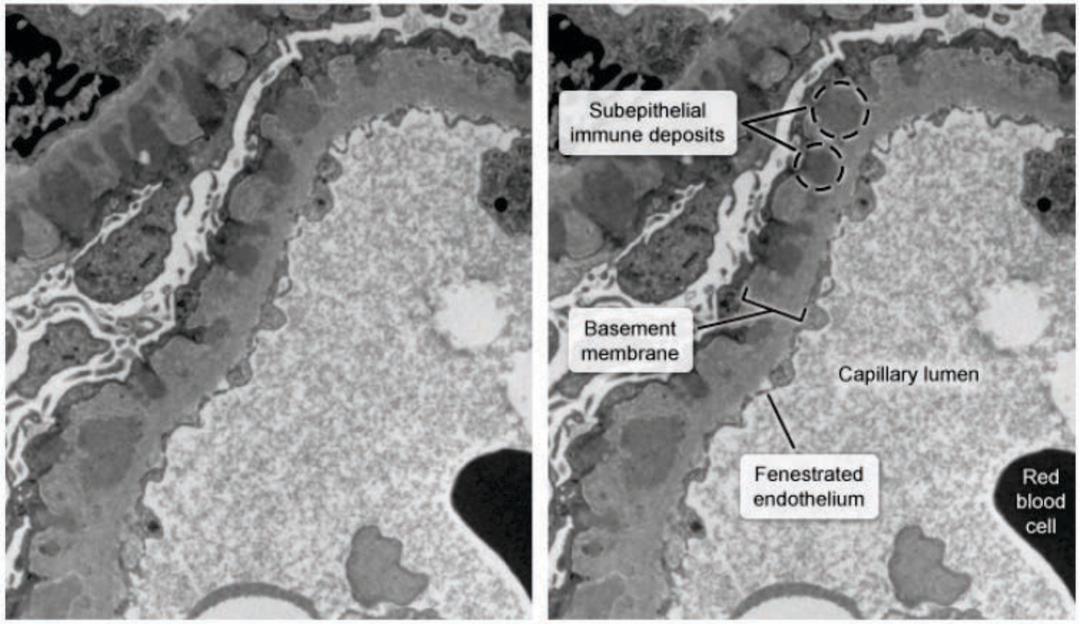
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Membranous nephropathy



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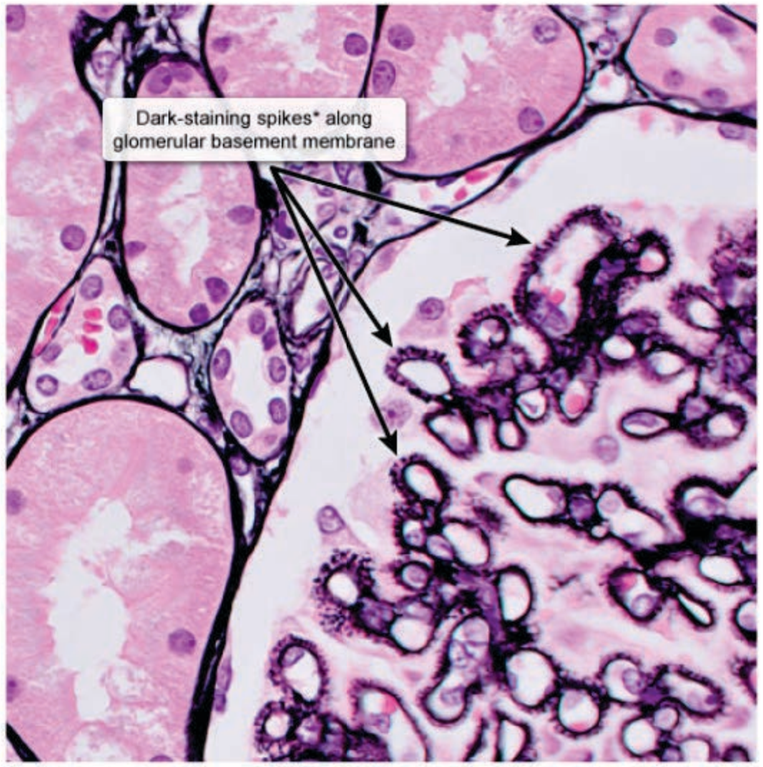
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(Choice G) Postinfectious glomerulonephritis occurs more commonly in children and causes a nephritic (not

Exhibit Display

Membranous nephropathy



Silver stain

*Projections of basement membrane material between immune complex deposits. ©UWorld

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This patient has **nephrotic syndrome** (ie, generalized edema, marked proteinuria). In conjunction with the
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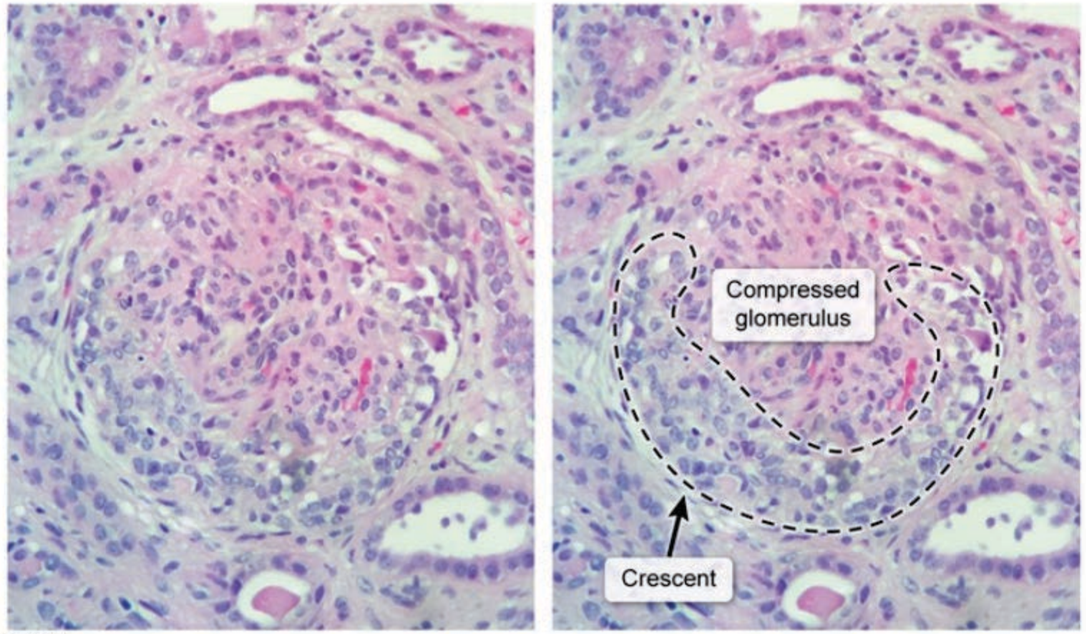
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(Choice G) Postinfectious glomerulonephritis occurs more commonly in children and causes a nephritic (not

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Crescentic glomerulonephritis



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diffuse thickening of the glomerular basement membrane (GBM) without an increase in glomerular cellularity.

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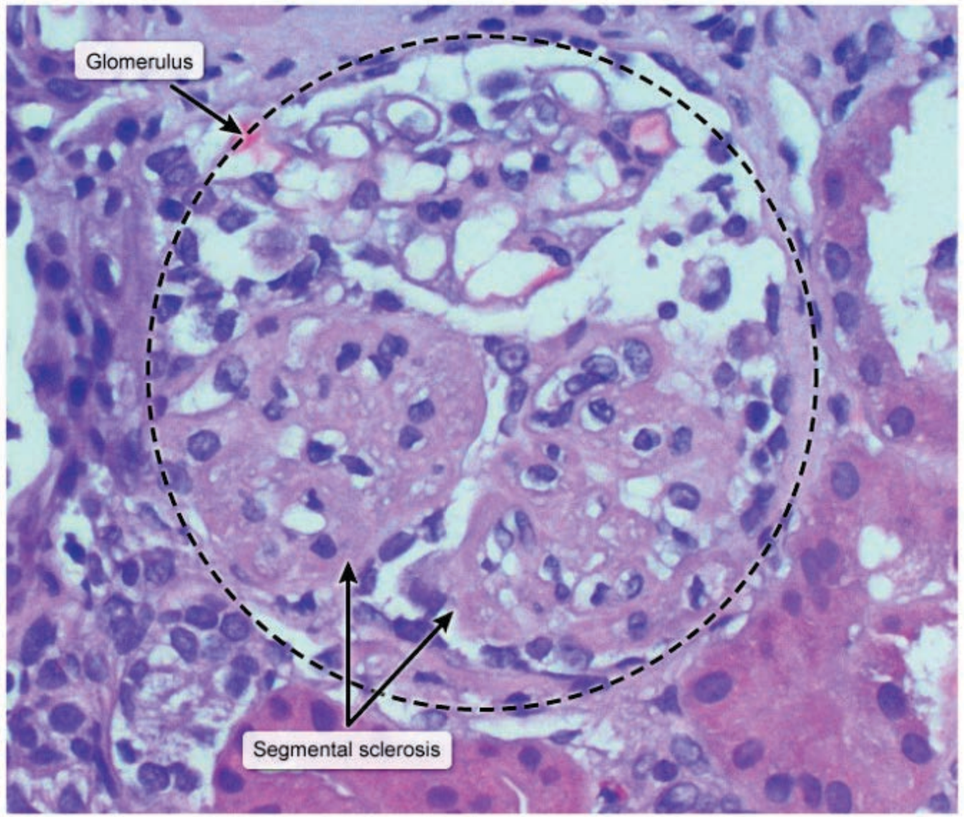
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demonstrates enlarged, diffusely hypercellular glomeruli.

Exhibit Display

Focal segmental glomerulosclerosis



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diffuse thickening of the glomerular basement membrane (GBM) without an increase in glomerular cellularity.

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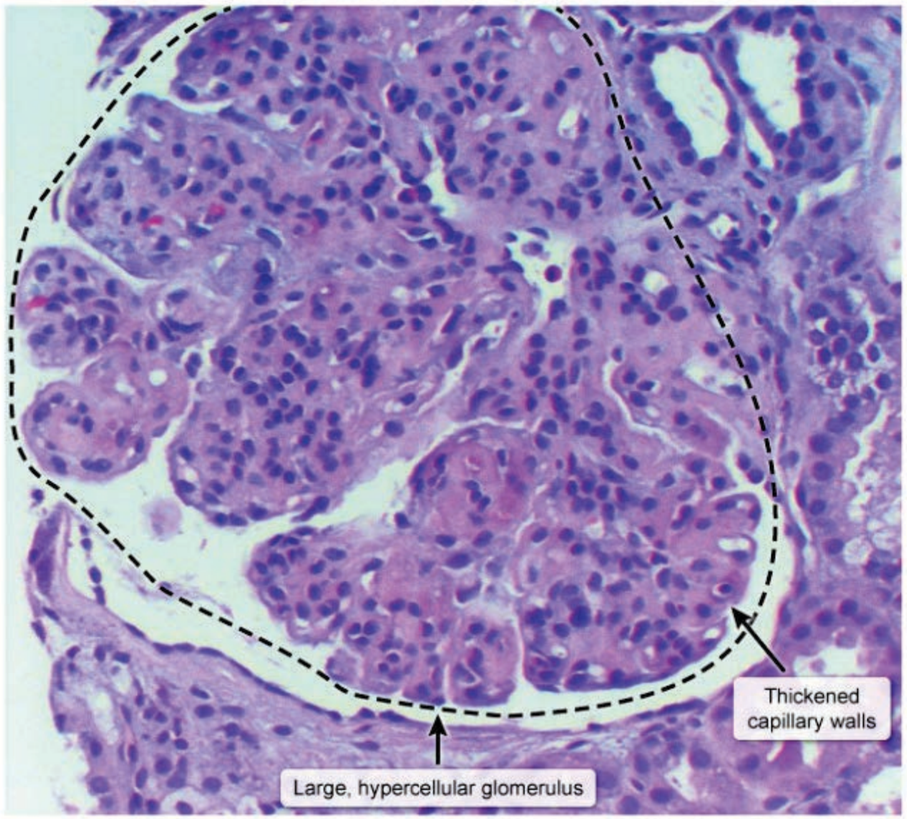
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Exhibit Display

Membranoproliferative glomerulonephritis



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through the deposits resemble **spikes and domes** when stained with a silver stain.

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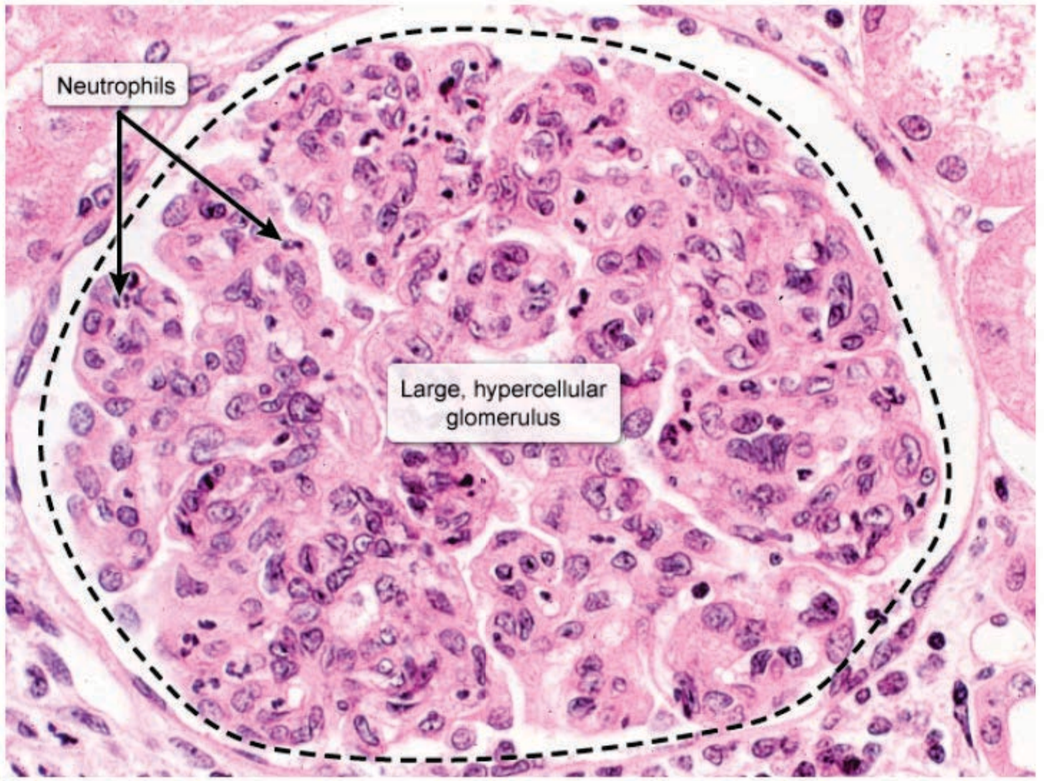
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solid malignancy, viral hepatitis, and systemic lupus erythematosus. Immune-complex deposition in the

Exhibit Display

Poststreptococcal glomerulonephritis



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A 62-year-old man is brought to the emergency department with a 1-hour history of sudden-onset severe headache and progressive lethargy. Medical history is significant for hypertension. Temperature is 37 C (98.6 F), blood pressure is 180/95 mm Hg, pulse is 60/min, and respirations are 10/min. On physical examination, the patient responds to painful stimuli only but does not move his left extremities to pain. The right pupil is larger than the left and is sluggish to react. CT scan of the head shows right basal ganglia hemorrhage causing compression of the right lateral ventricle and shift of the midline structures. Blood cell counts, serum chemistry studies, and coagulation profile are within normal limits. Endotracheal intubation is performed for airway protection, and an intravenous bolus of mannitol is administered. Which of the following is the most likely acute effect of the medication given to this patient?

	Serum sodium concentration	Renal tubular flow	Glomerular filtrate osmolality
A.	Decreased	Increased	Increased
B.	No change	Decreased	Increased
C.	Increased	No change	Increased
D.	Decreased	No change	Decreased
E.	No change	Decreased	Decreased

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		Serum sodium concentration	Renal tubular flow	Glomerular filtrate osmolality	
✓	A.	Decreased	Increased	Increased	(61%)
✗	B.	No change	Decreased	Increased	(6%)
	C.	Increased	No change	Increased	(15%)
	D.	Decreased	No change	Decreased	(14%)
	E.	No change	Decreased	Decreased	(3%)

Incorrect
Correct answer
A

61%
Answered correctly

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Time Spent

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Explanation

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Explanation

This patient with an acute **intraparenchymal hemorrhage** resulting in a midline shift was treated with **mannitol**. Mannitol, a sugar alcohol, is an osmotic diuretic that **increases plasma osmolality**, resulting in the flow of water down its concentration gradient from the intracellular space to the plasma. It does not cross the blood-brain barrier, therefore it is frequently used to treat elevated intracranial pressure because it draws water from the brain parenchyma into the vasculature, **reducing intracranial volume and pressure**.

As a result of the plasma volume expansion, the serum **sodium concentration decreases** (dilutional hyponatremia) and renal blood flow increases, resulting in **increased glomerular filtration** and **renal tubular flow**. Mannitol is freely filtered at the glomerulus but is not resorbed by the renal tubules; the resultant **hyperosmolar glomerular filtrate** reduces tubular reabsorption of free water, causing increased diuresis **(Choices D and E)**.

Dehydration (decreased total body free water) can eventually result if free water is not replaced after mannitol therapy, resulting in hypernatremia, elevated glomerular filtrate osmolality, and reduced renal tubular blood flow. However, this is a delayed effect that does not occur acutely following administration **(Choices B and C)**.

Educational objective:
Mannitol increases plasma osmolality, leading to the flow of water down its concentration gradient from the intracellular space to the plasma, helping to reduce intracranial pressure. The resulting plasma expansion also reduces serum sodium levels and increases glomerular filtration/tubular flow. Mannitol is freely filtered and not reabsorbed by the renal tubules, resulting in a hyperosmolar glomerular filtrate.

Pharmacology	Renal, Urinary Systems & Electrolytes	Mannitol
Subject	System	Topic

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A 60-year-old man comes to the office due to dark, rusty-colored urine for the last 2 weeks. He reports no pain, urinary frequency, or urgency. The patient has no chronic medical conditions and takes no medications. He smoked a half pack of cigarettes daily for 10 years but quit 30 years ago. His father had hypertension and his mother has Alzheimer dementia. Urinalysis shows a large number of red blood cells. Renal ultrasound reveals a mass in the right kidney. Cytologic evaluation of the mass shows malignant cells with a chromosome 3p deletion. The deletion most likely involves which of the following genes?

- A. *c-MYC*
- B. *NF-1*
- C. *RB*
- D. *VHL*
- E. *WT-1*

Submit

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A 60-year-old man comes to the office due to dark, rusty-colored urine for the last 2 weeks. He reports no pain, urinary frequency, or urgency. The patient has no chronic medical conditions and takes no medications. He smoked a half pack of cigarettes daily for 10 years but quit 30 years ago. His father had hypertension and his mother has Alzheimer dementia. Urinalysis shows a large number of red blood cells. Renal ultrasound reveals a mass in the right kidney. Cytologic evaluation of the mass shows malignant cells with a chromosome 3p deletion. The deletion most likely involves which of the following genes?

- A. *c-MYC* (7%)
- ✗ B. *NF-1* (2%)
- C. *RB* (5%)
- ✓ D. *VHL* (76%)
- E. *WT-1* (7%)

Incorrect
Correct answer
D

76%
Answered correctly

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Explanation

Common hereditary cancer syndromes			
Syndrome	**Gene**	**Associated neoplasms**	**Pathogenesis**
Lynch syndrome	*MSH2*, *MLH1*,	• Colorectal cancer • Endometrial cancer	

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Explanation

Common hereditary cancer syndromes			
Syndrome	**Gene**	**Associated neoplasms**	**Pathogenesis**
Lynch syndrome	*MSH2, MLH1, MSH6, PMS2*	• Colorectal cancer • Endometrial cancer • Ovarian cancer	• Autosomal dominant • Inactivating mutation in corresponding tumor suppressor gene • Deletion of remaining normal allele (second hit) leads to loss of heterozygosity & malignant transformation
Familial adenomatous polyposis	*APC*	• Colorectal cancer • Desmoids & osteomas • Brain tumors	
von Hippel-Lindau syndrome	*VHL*	• Hemangioblastomas • Clear cell renal carcinoma • Pheochromocytoma	
Li-Fraumeni syndrome	*TP53*	• Sarcomas • Breast cancer • Brain tumors • Adrenocortical carcinoma • Leukemia	
Multiple endocrine neoplasia type 1	*MEN1*	• Parathyroid adenomas • Pituitary adenomas	

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	MSH6, PMS2	• Ovarian cancer	
Familial adenomatous polyposis	*APC*	• Colorectal cancer • Desmoids & osteomas • Brain tumors	
von Hippel-Lindau syndrome	*VHL*	• Hemangioblastomas • Clear cell renal carcinoma • Pheochromocytoma	• Autosomal dominant • Inactivating mutation in corresponding tumor suppressor gene • Deletion of remaining normal allele (second hit) leads to loss of heterozygosity & malignant transformation
Li-Fraumeni syndrome	*TP53*	• Sarcomas • Breast cancer • Brain tumors • Adrenocortical carcinoma • Leukemia	
Multiple endocrine neoplasia type 1	*MEN1*	• Parathyroid adenomas • Pituitary adenomas • Pancreatic adenomas	
Multiple endocrine neoplasia type 2	*RET*	• Medullary thyroid cancer • Pheochromocytoma • Parathyroid hyperplasia (*MEN2A*)	• Autosomal dominant • Activating (gain-of-function) mutation in proto-oncogene • Continuous stimulation of cell division predisposes to tumor growth

This patient with hematuria and a malignant renal mass most likely has **renal cell carcinoma** (RCC). RCC

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This patient with hematuria and a malignant renal mass most likely has **renal cell carcinoma** (RCC). RCC, particularly the **clear cell subtype**, is strongly associated with deletion, nonsense, and frameshift mutations involving the **von Hippel-Lindau (*VHL*)** gene at chromosome 3p. The majority of RCCs are sporadic and develop as single tumors; these are typically associated with somatic mutations in the *VHL* gene. Germline *VHL* mutations also occur and are responsible for von Hippel-Lindau syndrome, a rare, autosomal dominant disorder characterized by clear cell renal carcinomas (often multifocal and bilateral), cerebellar hemangioblastoma, and pheochromocytoma.

VHL encodes a protein that normally inhibits hypoxia-inducible factors; *VHL* mutations lead to constitutive activation of these proteins, resulting in overexpression of multiple **angiogenic growth factors** (eg, VEG-F, PDG-F) that stimulate tumor proliferation. As a result, tumors harboring VHL mutations are highly sensitive to **angiogenesis inhibitors**.

(Choice A) *c-MYC* is an oncogene located on chromosome 8. Mutations are associated with Burkitt lymphoma and diffuse large B-cell lymphoma.

(Choice B) *NF-1* is a tumor suppressor gene located on chromosome 17. Mutations of this gene cause neurofibromatosis type 1.

(Choice C) The *RB* tumor suppressor gene (antioncogene) is located on chromosome 13. Mutations of this gene lead to the development of retinoblastoma and osteosarcoma.

(Choice E) Mutations of the *WT-1* tumor suppressor gene are associated with the development of Wilms tumor. This gene is located on chromosome 11.

Educational objective:
Sporadic and hereditary (associated with von Hippel-Lindau disease) renal cell carcinomas are associated with mutations involving the *VHL* gene on chromosome 3p. The *VHL* gene is a tumor suppressor that inhibits hypoxia-inducible factors; mutations lead to constitutive activation of these proteins, resulting in the activation of multiple

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involving the **von Hippel-Lindau (*VHL*)** gene at chromosome 3p. The majority of RCCs are sporadic and develop as single tumors; these are typically associated with somatic mutations in the *VHL* gene. Germline *VHL* mutations also occur and are responsible for von Hippel-Lindau syndrome, a rare, autosomal dominant disorder characterized by clear cell renal carcinomas (often multifocal and bilateral), cerebellar hemangioblastoma, and pheochromocytoma.

VHL encodes a protein that normally inhibits hypoxia-inducible factors; *VHL* mutations lead to constitutive activation of these proteins, resulting in overexpression of multiple **angiogenic growth factors** (eg, VEG-F, PDG-F) that stimulate tumor proliferation. As a result, tumors harboring VHL mutations are highly sensitive to **angiogenesis inhibitors**.

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(Choice E) Mutations of the *WT-1* tumor suppressor gene are associated with the development of Wilms tumor. This gene is located on chromosome 11.

Educational objective:
Sporadic and hereditary (associated with von Hippel-Lindau disease) renal cell carcinomas are associated with mutations involving the *VHL* gene on chromosome 3p. The *VHL* gene is a tumor suppressor that inhibits hypoxia-inducible factors; mutations lead to constitutive activation of these proteins, resulting in the activation of multiple angiogenic and tumorigenic growth factors (eg, VEG-F, PDG-F).

References

- VHL and hypoxia signaling: beyond HIF in cancer

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A 70-year-old man comes to the office for follow-up of hypertension. He has been taking amlodipine but his recent home blood pressure readings have been elevated. The patient has a long smoking history and, despite many attempts at quitting, continues to smoke cigarettes. Blood pressure is 140/90 mm Hg and pulse is 76/min. Examination shows a bruit on auscultation of the abdomen. Further evaluation reveals bilateral renal artery stenosis. After initial discussion, the patient is started on daily lisinopril therapy. The patient is advised to return to the clinic in a few days. The close follow-up is recommended due to which of the following anticipated effects in this patient's kidney function?

	Renal perfusion	Intraglomerular pressure	Filtration fraction
A.	Decreased	Decreased	Decreased
B.	Decreased	Increased	Increased
C.	Increased	Decreased	Decreased
D.	Increased	Increased	Decreased
E.	Increased	Increased	Increased

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	Renal perfusion	Intraglomerular pressure	Filtration fraction	
✓ A.	Decreased	Decreased	Decreased	(37%)
✗ B.	Decreased	Increased	Increased	(10%)
C.	Increased	Decreased	Decreased	(38%)
D.	Increased	Increased	Decreased	(5%)
E.	Increased	Increased	Increased	(7%)

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Correct answer
A

37%
Answered correctly

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Explanation

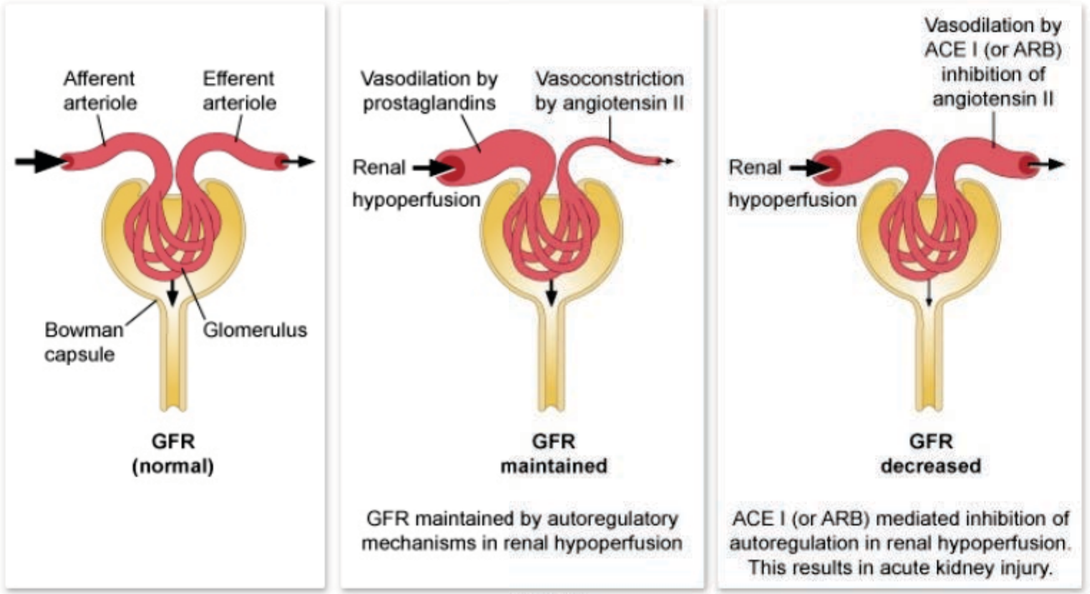
Glomerular filtration rate autoregulatory mechanisms

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Glomerular filtration rate autoregulatory mechanisms



ARB = angiotensin II receptor blocker; **GFR** = glomerular filtration rate.

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angiotensin-aldosterone system. **Angiotensin II**, a potent vasoconstrictor, increases systemic pressure and

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This patient has **bilateral renal artery stenosis** (RAS) and is at risk for acute renal failure with the initiation of an ACE inhibitor. Bilateral RAS, which typically occurs in older patients with widespread atherosclerosis, results in a reduction of renal perfusion. This leads to a lowered glomerular filtration rate (GFR) and activation of the renin-angiotensin-aldosterone system. **Angiotensin II**, a potent vasoconstrictor, increases systemic pressure and preferentially constricts the efferent arteriole, which increases intraglomerular hydrostatic pressure to maintain adequate GFR. The filtration fraction (FF)—the ratio of GFR to renal plasma flow (RPF) (FF = GFR/RPF)—is increased as the GFR remains relatively preserved despite the decreased RPF.

ACE inhibitors (eg, lisinopril) lower angiotensin II levels, causing a reduction in systemic pressures and relative dilation of the efferent arteriole. In patients with bilateral RAS, the reduced systemic pressures are no longer high enough to overcome the stenosis, and **renal blood flow drops**. The dilation of the efferent arteriole leads to a **reduction of intraglomerular filtration pressure**, which results in the **reduction of GFR and filtration fraction**.

Although patients with bilateral RAS treated with ACE inhibitors are at risk for acute renal failure, most patients can tolerate the medication with only a mild (<30%) rise in serum creatinine. In addition, risk can be reduced with discontinuation of diuretics, as volume depletion increases the dependence on efferent arteriolar constriction to maintain GFR.

Educational objective:
Patients with bilateral renal artery stenosis have reduced renal perfusion (due to atherosclerotic blockage) and are dependent upon angiotensin II-induced efferent vasoconstriction to maintain glomerular filtration rate. ACE inhibitors block angiotensin II-mediated vasoconstriction, which can reduce systemic blood pressure and lower renal perfusion. In addition, ACE inhibitors cause dilation of the efferent arteriole, leading to a reduction in glomerular filtration rate and renal filtration fraction.

Pharmacology	Renal, Urinary Systems & Electrolytes	ACE inhibitors
Subject	System	Topic

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GFR maintained by autoregulatory mechanisms in renal hypoperfusion

ACE I (or ARB) mediated inhibition of autoregulation in renal hypoperfusion. This results in acute kidney injury

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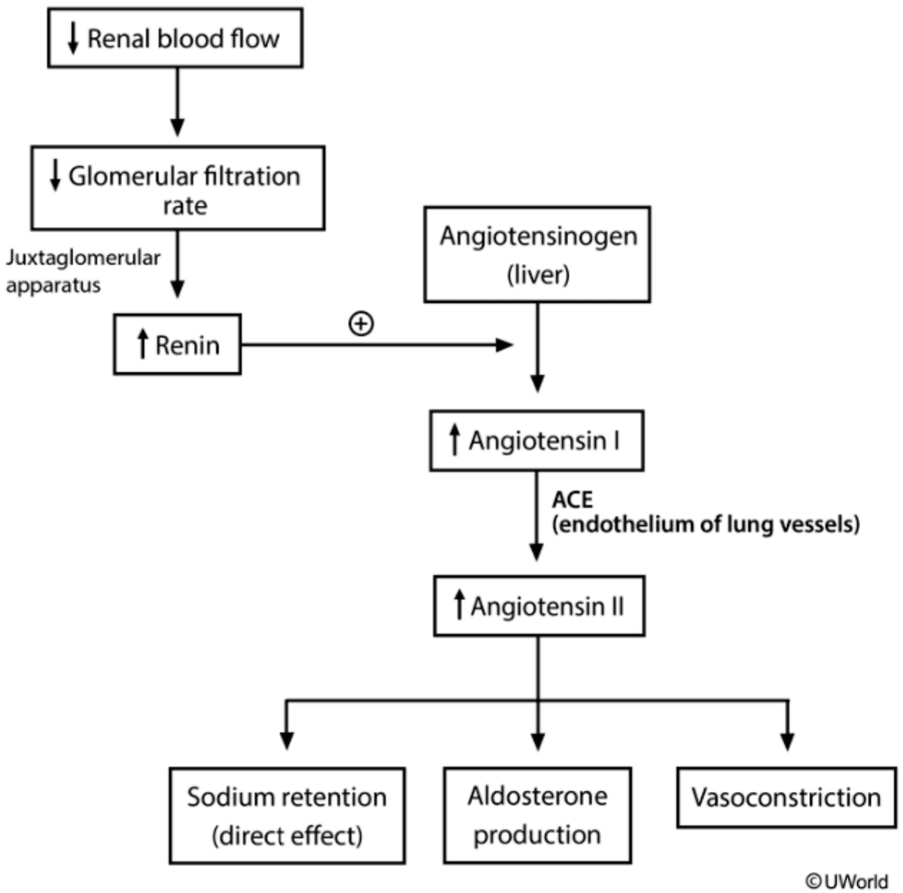
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A 28-year-old man comes to the physician with muscle weakness and headaches for the last 2 months. He denies palpitations, tremors, or increased sweating. His blood pressure is 190/120 mm Hg and his pulse is 68/min. His serum potassium level is 2.8 mEq/L. The patient's plasma renin activity is high and his serum aldosterone levels are elevated. A 24-hour urine collection shows increased potassium excretion. Which of the following is the most likely cause of this patient's symptoms?

- A. Adrenal cortical tumor
- B. Adrenal medullary tumor
- C. Juxtaglomerular cell tumor
- D. Pituitary tumor
- E. Primary hypertension

Submit

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- A. Adrenal cortical tumor (21%)
- ✗ B. Adrenal medullary tumor (5%)
- ✓ C. Juxtaglomerular cell tumor (64%)
- D. Pituitary tumor (4%)
- E. Primary hypertension (3%)

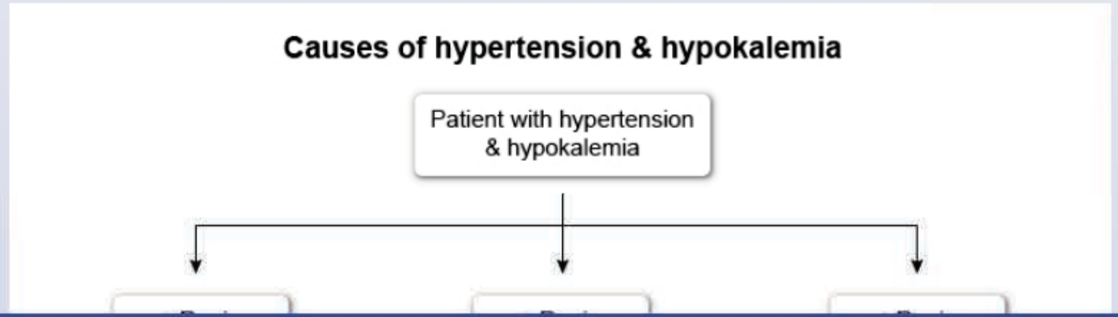
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Answered correctly

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Explanation



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Exhibit Display

Causes of hypertension & hypokalemia

Patient with hypertension & hypokalemia

↑ Renin ↑ Aldosterone	↓ Renin ↑ Aldosterone	↓ Renin ↓ Aldosterone
Secondary hyperaldosteronism	**Primary hyperaldosteronism**	**Non-aldosterone causes**
• Renovascular hypertension • Malignant hypertension • Renin-secreting tumor • Diuretic use	• Aldosterone-producing tumor • Bilateral adrenal hyperplasia	• Congenital adrenal hyperplasia • Deoxycorticosterone-producing adrenal tumor • Cushing syndrome • Exogenous mineralocorticoids

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(Choice A).

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This patient has **elevated serum aldosterone**, a known cause of hypertension, hypokalemia, and muscle weakness. Hyperaldosteronism can be divided into primary and secondary etiologies. In **primary hyperaldosteronism** (ie, Conn's syndrome), an adrenal adenoma or bilateral adrenal hyperplasia causes excessive and unchecked aldosterone production that leads to feedback inhibition of renin secretion (ie, **low renin** level). Primary hyperaldosteronism can be excluded in this patient due to his increased plasma renin activity **(Choice A)**.

In **secondary hyperaldosteronism**, overproduction of aldosterone occurs secondary to increased renin synthesis, resulting in **elevated renin** and aldosterone levels. Causes of secondary hyperaldosteronism include **renal artery stenosis** (typically associated with fibromuscular dysplasia or atherosclerosis), diuretic use, malignant hypertension (which leads to microvascular damage and renal ischemia), and renin-secreting tumors. Renin-secreting tumors (reninomas) are rare, small, solitary, benign **juxtaglomerular cell neoplasms**. Reninomas should be strongly considered in patients with marked hyperreninemia and hypertension who clearly do not have renovascular disease.

(Choice B) Pheochromocytomas are adrenal medullary tumors that secrete excessive catecholamines. High epinephrine levels can sometimes cause hypokalemia via β2-receptor stimulation and the resulting intracellular K^+ shift. However, patients with pheochromocytomas typically present with episodic headaches, tachycardia (often sensed as palpitations), and increased sweating.

(Choice D) A pituitary tumor (eg, an ACTH-secreting adenoma causing Cushing's disease) can result in secondary hypertension due to excess adrenal glucocorticoids (increases vascular sensitivity to adrenergic agents). The resulting hypertension suppresses the renin-angiotensin-aldosterone axis, leading to low levels of renin and aldosterone.

(Choice E) Primary (essential) hypertension is not typically associated with severe hypertension, elevated levels of renin, or hypokalemia.

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excessive and unchecked aldosterone production that leads to feedback inhibition of renin secretion (ie, **low renin** level). Primary hyperaldosteronism can be excluded in this patient due to his increased plasma renin activity **(Choice A)**.

In **secondary hyperaldosteronism**, overproduction of aldosterone occurs secondary to increased renin synthesis, resulting in **elevated renin** and aldosterone levels. Causes of secondary hyperaldosteronism include **renal artery stenosis** (typically associated with fibromuscular dysplasia or atherosclerosis), diuretic use, malignant hypertension (which leads to microvascular damage and renal ischemia), and renin-secreting tumors. Renin-secreting tumors (reninomas) are rare, small, solitary, benign **juxtaglomerular cell neoplasms**. Reninomas should be strongly considered in patients with marked hyperreninemia and hypertension who clearly do not have renovascular disease.

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(Choice E) Primary (essential) hypertension is not typically associated with severe hypertension, elevated levels of renin, or hypokalemia.

Educational objective:
Elevated serum aldosterone levels can manifest with hypertension, hypokalemia, and muscle weakness. Increased levels of both renin and aldosterone are indicative of secondary hyperaldosteronism, which can be caused by renovascular disease and renin-secreting tumors.

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This patient has **elevated serum aldosterone**, a known cause of hypertension, hypokalemia, and muscle weakness. Hyperaldosteronism can be divided into primary and secondary etiologies. In **primary hyperaldoster**
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(Choice A).

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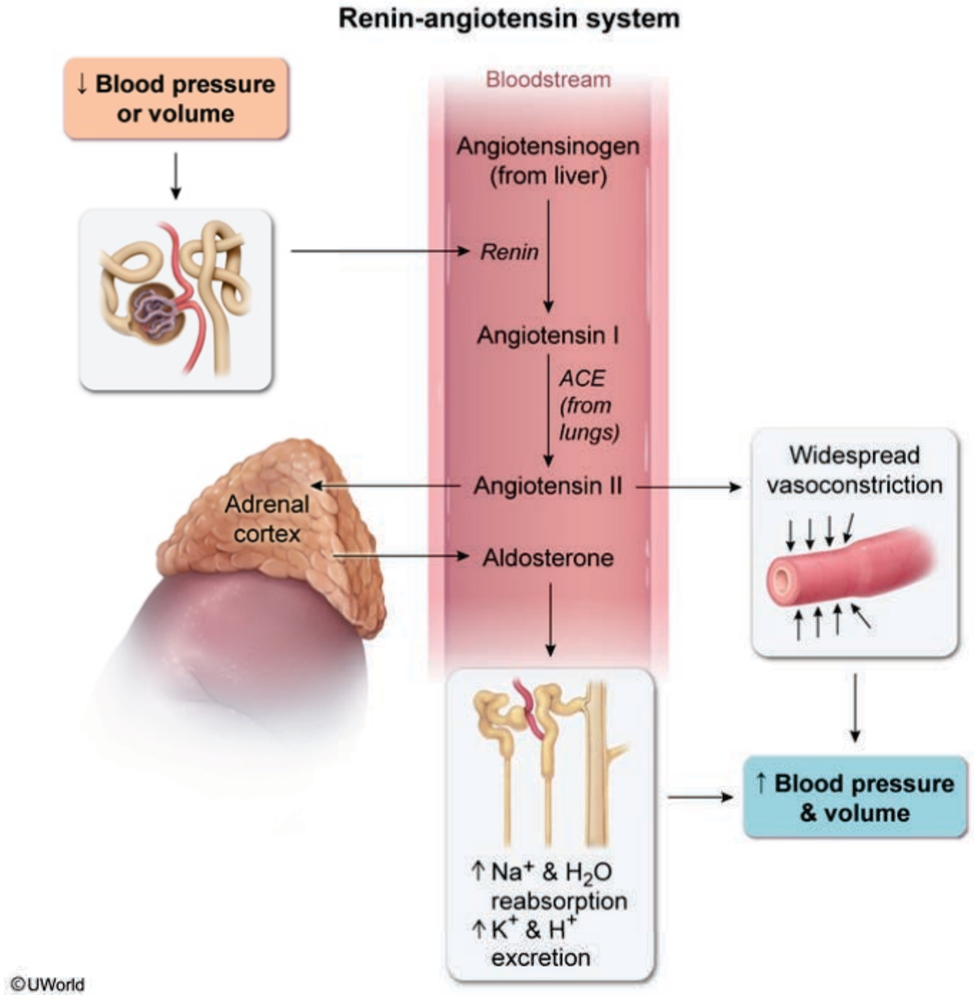
(Choice B) Ph
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(Choice D) A
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(Choice E) Pr
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Educational o

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A 55-year-old woman with stage IV chronic kidney disease due to type 2 diabetes mellitus comes to the office for a follow-up visit. Blood pressure is 140/90 mm Hg and pulse is 78/min. BMI is 31 kg/m^2. Laboratory results are as follows:

Hemoglobin	10.5 g/dL
Calcium	8.8 mg/dL
Albumin	3.7 g/dL
Phosphorus	7.2 mg/dL
Creatinine	3.3 mg/dL
Blood urea nitrogen	88 mg/dL
Parathyroid hormone	100 pg/mL (normal: 10-65)

The patient's serum phosphorus has been persistently elevated despite strict dietary phosphate restriction. Treatment with sevelamer is initiated. This medication reduces the serum phosphorus level by which of the following mechanisms?

- A. Blocking of vitamin D receptors
- B. Decreased intestinal absorption of phosphorus
- C. Reduction of proximal renal tubular reabsorption of phosphorus
- D. Stimulation of fibroblast growth factor 23 release
- E. Suppression of parathyroid hormone secretion
- F. Transcellular movement of phosphorus

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follows:

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Albumin	3.7 g/dL
Phosphorus	7.2 mg/dL
Creatinine	3.3 mg/dL
Blood urea nitrogen	88 mg/dL
Parathyroid hormone	100 pg/mL (normal: 10-65)

The patient's serum phosphorus has been persistently elevated despite strict dietary phosphate restriction. Treatment with sevelamer is initiated. This medication reduces the serum phosphorus level by which of the following mechanisms?

- ✗ A. Blocking of vitamin D receptors (2%)
- ✓ B. Decreased intestinal absorption of phosphorus (60%)
- C. Reduction of proximal renal tubular reabsorption of phosphorus (18%)
- D. Stimulation of fibroblast growth factor 23 release (7%)
- E. Suppression of parathyroid hormone secretion (7%)
- F. Transcellular movement of phosphorus (3%)

Incorrect
Correct answer
B

60%
Answered correctly

04 secs
Time Spent

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Explanation

Chronic kidney disease (CKD) often causes **hyperphosphatemia** due to the impaired ability of the kidneys to excrete phosphorus. Hyperphosphatemia is thought to be the inciting event in the onset of CKD-related mineral bone disorder. Elevated blood phosphate triggers the release of fibroblast growth factor 23 from bone, which lowers calcitriol production and intestinal calcium absorption. Reduced circulating calcium, along with hyperphosphatemia, leads to secondary hyperparathyroidism.

Dietary phosphorus restriction is recommended for patients with CKD. However, oral **phosphate binders** are usually needed if dietary restriction is not sufficient to lower phosphate levels. Phosphate binders can be calcium containing (eg, calcium carbonate/acetate) or non–calcium containing (eg, sevelamer, lanthanum). **Sevelamer** is a **nonabsorbable anion-exchange resin** that binds intestinal phosphate to **reduce systemic absorption**. The resulting complex is eliminated in the feces.

(Choice A) Vitamin D receptor antagonists are largely experimental compounds that have been considered for the treatment of Paget disease of bone. Most patients with CKD benefit from vitamin D supplementation due to decreased renal formation of 1,25-dihydroxyvitamin D.

(Choices C, D, and F) Parathyroid hormone induces internalization and destruction of type IIa sodium/phosphate cotransporters (NPT2) in the proximal renal tubule. *NPT2* gene expression is downregulated by fibroblast growth factor 23. These processes lead to decreased transcellular transport (and therefore decreased reabsorption) of phosphate in the renal tubules.

(Choice E) Parathyroid hormone functions to reduce phosphate reabsorption by the kidney; reduced secretion would worsen, not correct, hyperphosphatemia. Sevelamer reduces circulating serum phosphorus by blocking intestinal absorption, which helps to mitigate secondary hyperparathyroidism.

Educational objective:
Chronic kidney disease can cause hyperphosphatemia due to decreased renal excretion of phosphorus. Dietary

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excrete phosphorus. Hyperphosphatemia is thought to be the inciting event in the onset of CKD-related mineral bone disorder. Elevated blood phosphate triggers the release of fibroblast growth factor 23 from bone, which lowers calcitriol production and intestinal calcium absorption. Reduced circulating calcium, along with hyperphosphatemia, leads to secondary hyperparathyroidism.

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(Choice A) Vitamin D receptor antagonists are largely experimental compounds that have been considered for the treatment of Paget disease of bone. Most patients with CKD benefit from vitamin D supplementation due to decreased renal formation of 1,25-dihydroxyvitamin D.

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Educational objective:
Chronic kidney disease can cause hyperphosphatemia due to decreased renal excretion of phosphorus. Dietary phosphorus restriction is recommended, but oral phosphate binders are often needed. Sevelamer is a nonabsorbable anion-exchange resin that binds intestinal phosphate to reduce absorption.

References

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A researcher is studying the effect of various manipulations on kidney blood flow and glomerular filtration. Which of the following is most likely to both decrease renal plasma flow and increase the filtration fraction?

- A. Hyperproteinemia
- B. Bladder neck obstruction
- C. Constriction of the efferent arteriole
- D. Constriction of the afferent arteriole
- E. Dilation of the efferent arteriole

Submit

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A researcher is studying the effect of various manipulations on kidney blood flow and glomerular filtration. Which of the following is most likely to both decrease renal plasma flow and increase the filtration fraction?

- A. Hyperproteinemia (1%)
- ✕ B. Bladder neck obstruction (1%)
- ✓ C. Constriction of the efferent arteriole (82%)
- D. Constriction of the afferent arteriole (11%)
- E. Dilation of the efferent arteriole (2%)

Incorrect
Correct answer
C

82%
Answered correctly

04 secs
Time Spent

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Explanation

Constriction of the efferent (outgoing) arteriole will impede blood flow through the kidney. This will decrease RPF, but will increase glomerular capillary hydrostatic pressure as the fluid "backs up" in the glomerulus, increasing hydrostatic pressure. This increased glomerular hydrostatic pressure will cause an increase in the filtration fraction.

The renal plasma flow (RPF) is the volume of plasma that is delivered to the kidney per unit time. The RPF is provided by the renal blood flow, which delivers both erythrocytes and plasma to the kidney. The RPF is theoretically calculated by subtracting the amount of erythrocytes (hematocrit) from the total renal blood flow. Clinically, however, RPF is generally estimated by calculating the paraaminohippuric acid (PAH) clearance. RPF is linked to the glomerular filtration rate (GFR) and the filtration fraction (FF) by the following equation:

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$$FF = GFR / RPF$$

The filtration fraction refers to the proportion of the RPF that is filtered from the glomerular capillaries into Bowman's space and is expressed as a percentage. Using the equation above, one can observe that increases in GFR or decreases in RPF will increase the FF. The GFR is dependent on hydrostatic and oncotic pressures in the glomerular capillaries and Bowman's space and can be calculated with the following equation:

$$GFR = K_f ((P_G - P_B) - (\pi_G - \pi_B))$$

Where Kf refers to the coefficient of filtration, P_G refers to the hydrostatic pressure in the glomerular capillaries, P_B refers to the hydrostatic pressure in Bowman's space, π_G refers to the oncotic pressure in the glomerular capillaries and π_B refers to the oncotic pressure in Bowman's space. Increases in the glomerular capillary hydrostatic pressure or the Bowman's space oncotic pressure will increase GFR, while increases in capillary oncotic pressure or Bowman's space hydrostatic pressure will decrease GFR.

(Choice A) Hyperproteinemia causes increased glomerular capillary oncotic pressure thereby decreasing GFR. This will have no effect on the RPF, but will cause a decreased FF due to the decreased GFR.

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glomerular capillaries and Bowman's space and can be calculated with the following equation:

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(Choice A) Hyperproteinemia causes increased glomerular capillary oncotic pressure thereby decreasing GFR. This will have no effect on the RPF, but will cause a decreased FF due to the decreased GFR.

(Choice B) Bladder neck obstruction causes an increase in Bowman's space hydrostatic pressure thereby decreasing GFR. This too will have no effect on the RPF, but will cause a decreased FF due to the decreased GFR.

(Choice D) Constriction of the afferent (incoming) arteriole causes a decrease in glomerular capillary hydrostatic pressure leading to a decreased GFR. RPF is also decreased by this process. The FF remains unchanged due to decreases in both GFR and RPF.

(Choice E) Dilation of the efferent arteriole causes decreased glomerular capillary hydrostatic pressure leading to a decrease in GFR. The RPF is increased by this process, and the FF is decreased due to the decrease in GFR and increase in RPF.

Educational Objective:
Increases in the capillary hydrostatic pressure or the Bowman's space oncotic pressure will increase GFR, while increases in capillary oncotic pressure or Bowman's space hydrostatic pressure will decrease GFR. The filtration fraction (FF) can be calculated by dividing the GFR by the renal plasma flow (RPF). Increases in GFR or decreases in RPF will increase the FF.

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A 59-year-old man who is being treated for hypercholesterolemia, diabetes, and hypertension comes to the physician for a scheduled follow-up visit three weeks after starting a new medication. He has no new complaints. Blood work drawn yesterday shows an interim increase in potassium from 4.8 mEq/L to 5.2 mEq/L and a creatinine elevation from 1.2 mg/dL to 1.6 mg/dL. Administration of which of the following drugs is most likely responsible for the change in this patient's renal function?

- A. Lisinopril
- B. Metoprolol
- C. Atorvastatin
- D. Hydrochlorothiazide
- E. Furosemide
- F. Metformin
- G. Prazosin

Submit

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A 59-year-old man who is being treated for hypercholesterolemia, diabetes, and hypertension comes to the physician for a scheduled follow-up visit three weeks after starting a new medication. He has no new complaints. Blood work drawn yesterday shows an interim increase in potassium from 4.8 mEq/L to 5.2 mEq/L and a creatinine elevation from 1.2 mg/dL to 1.6 mg/dL. Administration of which of the following drugs is most likely responsible for the change in this patient's renal function?

- ✓ A. Lisinopril (61%)
- B. Metoprolol (3%)
- ✗ C. Atorvastatin (7%)
- D. Hydrochlorothiazide (7%)
- E. Furosemide (6%)
- F. Metformin (11%)
- G. Prazosin (1%)

Incorrect
Correct answer
A

61%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Angiotensin-converting enzyme (ACE) inhibitors (typically named "-pril") are one of the most important agents in treating hypertension, heart failure, and renal failure with or without proteinuria. They work by preventing the conversion of angiotensin I to angiotensin II. This prevents the efferent arteriole from constricting more than the afferent arteriole, thus decreasing the glomerular pressure and glomerular filtration rate (GFR). It is expected for

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(Choice B) Metoprolol is a beta-blocker. Typical side-effects include bradycardia and erectile dysfunction. Although beta blockers act upon the beta-1 receptors of the juxtaglomerular cells to reduce renin secretion, their use generally does not have a clinically significant effect on the GFR.

(Choice C) Atorvastatin is an HMG-CoA reductase inhibitor; worrisome side-effects include muscle toxicity and hepatic dysfunction. Statins can uncommonly cause rhabdomyolysis, particularly when used in combination with fibrates or cyclosporin. However, massive rhabdomyolysis leading to acute kidney injury would most likely produce additional signs and symptoms such as myalgias, muscle weakness, dark urine, and elevated creatine kinase.

(Choices D and E) Hydrochlorothiazide is a *potassium-wasting* thiazide diuretic that may decrease GFR if it results in volume depletion and pre-renal azotemia. Furosemide is also *potassium-wasting* loop diuretic.

(Choice F) Metformin itself does not have nephrotoxic side effects. However, impaired renal function or recent IV contrast administration may reduce metformin excretion, resulting in systemic accumulation and possible lactic acidosis.

(Choice G) Prazosin is an alpha-1 adrenergic antagonist that is used in the treatment of hypertension. It does not decrease the GFR.

Educational objective:
Common side-effects of ACE-inhibitors include decreased glomerular filtration rate (GFR), hyperkalemia, and

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conversion of angiotensin I to angiotensin II. This prevents the efferent arteriole from constricting more than the afferent arteriole, thus decreasing the glomerular pressure and glomerular filtration rate (GFR). It is expected for the GFR to decrease in all patients initially. Most clinicians are generally not concerned by this unless the creatinine increases by greater than 30% because the long-term benefits of ACE inhibitors are well studied. Other common side-effects of ACE inhibitors include hyperkalemia and cough.

(Choice B) Metoprolol is a beta-blocker. Typical side-effects include bradycardia and erectile dysfunction. Although beta blockers act upon the beta-1 receptors of the juxtaglomerular cells to reduce renin secretion, their use generally does not have a clinically significant effect on the GFR.

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(Choice F) Metformin itself does not have nephrotoxic side effects. However, impaired renal function or recent IV contrast administration may reduce metformin excretion, resulting in systemic accumulation and possible lactic acidosis.

(Choice G) Prazosin is an alpha-1 adrenergic antagonist that is used in the treatment of hypertension. It does not decrease the GFR.

Educational objective:
Common side-effects of ACE-inhibitors include decreased glomerular filtration rate (GFR), hyperkalemia, and cough. Angioedema is a rare, but life-threatening, side-effect.

Pharmacology	Renal, Urinary Systems & Electrolytes	Hyperkalemia
Subject	System	Topic

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A 62-year-old woman comes to the office for medical evaluation. The patient states her 26-year-old son has developed renal failure from chronic glomerulonephritis and is undergoing dialysis therapy. She has the same blood group as her son and she wants to donate one of her kidneys to him. The patient has no chronic medical conditions and takes no medications. Vital signs are within normal limits, and physical examination shows no abnormalities. The patient understands that she may not be a compatible donor based on human leukocyte antigen (HLA) testing. In addition, which of the following age-related renal changes should be taken into consideration when assessing donor suitability?

- A. Decreased number of functional glomeruli
- B. Decreased solute excreting ability
- C. Increased creatinine clearance
- D. Increased renal blood flow
- E. Increased sensitivity for renin release

Submit

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- ✓ A. Decreased number of functional glomeruli (62%)
- ✗ B. Decreased solute excreting ability (23%)
- C. Increased creatinine clearance (9%)
- D. Increased renal blood flow (1%)
- E. Increased sensitivity for renin release (3%)

Incorrect
Correct answer
A

62%
Answered correctly

03 secs
Time Spent

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Explanation

Normal aging results in multiple physiologic and structural alterations that lead to a slow decline in renal function, even in the absence of renal disease. These alterations typically begin around age 30, with a more marked decline occurs in those >50 years, resulting in the predisposition of elderly patients to develop acute kidney injury or chronic kidney disease. These alterations include:

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- **Reduced renal mass and functional glomeruli:** There is a 50% reduction in functional glomeruli by age 75 associated with a reduction in renal mass due to atrophy and fibrotic replacement. This results in **reduced glomerular filtration rate and creatinine clearance**, as well as a reduced ability to concentrate urine, which may predispose patients to hypovolemia during periods of stress **(Choice C)**.
- **Reduced renal blood flow (RBF):** Loss of renal microvasculature results in a reduction in renal blood flow with age, increasing the susceptibility to ischemic injury **(Choice D)**. Furthermore, RBF becomes more dependent upon prostaglandins to maintain adequate blood flow, leading to increased susceptibility to renal injury with nonsteroidal anti-inflammatory drugs (due to reduced prostaglandin formation).
- **Reduced hormonal responsiveness:** There is reduced secretion of renin (blunts the renin-angiotensin-aldosterone system response) and reduced hydroxylation of vitamin D in response to parathyroid hormone **(Choice E)**. However, unlike chronic renal disease, the production of erythropoietin in response to anemia or hypoxemia is unchanged.

Older kidneys also have a higher proportion of cells that undergo apoptosis after a given insult (eg, ischemia) and are less capable of regeneration.

(Choice B) The ability to excrete solutes is relatively preserved in the aging kidney.

Educational objective:
Normal aging results in multiple physiologic and structural alterations that lead to a slow decline in renal function. These include reductions in renal mass and functional glomeruli (ie, reduced glomerular filtration rate and creatinine clearance), decreased renal blood flow, and limited hormonal responsiveness (eg, renin, parathyroid

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A 46-year-old woman is admitted to the hospital with dehydration secondary to excess output from an ileostomy. Five years ago, the patient had a total colectomy with a diverting ileostomy for colon cancer. For the last 6 months, she has had increased output from the ileostomy and has been admitted to the hospital twice with similar episodes of dehydration. On the second day of admission, she reports right flank pain. X-ray of the abdomen reveals a nonspecific bowel gas pattern with no evidence of renal calculi. Ultrasound of the abdomen shows a 4-mm stone in the distal right ureter. The patient is treated with analgesics and the stone passes spontaneously. Microscopic analysis of the stone reveals a pure uric acid stone. Which of the following is the most likely underlying mechanism leading to stone formation in this patient?

- A. Bile salt malabsorption in the ileum
- B. Concentrated acidic urine
- C. Increased uric acid production
- D. Infection with urea-splitting bacteria
- E. Overproduction of parathyroid hormone

Submit

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- A. Bile salt malabsorption in the ileum (18%)
- ✓ B. Concentrated acidic urine (51%)
- C. Increased uric acid production (20%)
- D. Infection with urea-splitting bacteria (8%)
- E. Overproduction of parathyroid hormone (1%)

Correct

51% Answered correctly

03 secs Time Spent

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Explanation

Uric acid kidney stones	
	• Low urine pH: chronic diarrhea (GI bicarbonate loss), metabolic syndrome/ diabetes mellitus

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Uric acid kidney stones	
Risk factors	• Low urine pH: chronic diarrhea (GI bicarbonate loss), metabolic syndrome/ diabetes mellitus • Increased uric acid excretion: gout, myeloproliferative disorders • Increased urine concentration: hot, arid climates; dehydration
Pathophysiology	• Acidic urine favors formation of uric acid (insoluble) over urate (soluble) • Supersaturation of urine with uric acid precipitates crystal formation
Clinical characteristics	• Radiolucent stones (not visible on x-ray) • Uric acid crystals on urine microscopy (diamond/rhomboid shaped) • Urine pH usually <5.5
Treatment	• Alkalinization of urine (eg, potassium citrate) • Reduction of uric acid production (eg, low-purine diet, allopurinol)
GI = gastrointestinal.	

This patient with recurrent episodes of **dehydration** due to fluid loss from her ileostomy developed a uric acid stone. Pure uric acid stones are radiolucent and cannot be visualized on x-ray but appear as yellow/brown agglomerations of rhomboid-shaped crystals on gross/microscopic examination. Biochemical risk factors include low urine pH, low urine volume (eg, dehydration), and hyperuricemia.

Patients with **chronic diarrhea** or those who have had a colectomy have reduced bicarbonate reabsorption from the gut, leading to a state of chronic metabolic acidosis. The kidneys compensate by increasing the **excretion of hydrogen ions** (H^+) and reabsorption of bicarbonate in the collecting ducts. This lowers urine pH (**acidic urine**), increasing the conversion of soluble urate ion into **insoluble uric acid**. Conversely, alkalinization of the urine with potassium citrate favors formation of urate and can prevent, and in some cases dissolve, uric acid stones. Other

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(Choice A) Dietary calcium and oxalate normally form insoluble complexes, which are eliminated in the feces. Disruption of the normal enterohepatic circulation of bile acids can cause malabsorption of dietary lipids, which then form soap complexes with calcium, allowing increased absorption of free oxalate. The excess oxalate is then excreted by the kidneys where it promotes formation of calcium oxalate stones. These stones are radio-opaque.

(Choice C) Overproduction of uric acid (eg, gout, myeloproliferative disorders) can lead to uric acid stones. However, this patient has no features of these disorders, and her stone formation is likely due to abnormally concentrated and acidic urine.

(Choice D) Hydrolysis of urea by urease-producing bacteria (eg, *Proteus*, *Klebsiella*) yields ammonia, which alkalinizes the urine and promotes formation of magnesium ammonium phosphate (struvite) stones. These stones are large and radio-opaque, and typically present with fever and moderate flank pain.

(Choice E) Hyperparathyroidism leads to hypercalcemia and an increased filtered calcium load. The subsequent hypercalciuria increases the risk of radio-opaque calcium (oxalate, phosphate) stones.

Educational objective:

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Educational objective:
Formation of uric acid kidney stones is promoted by low urine pH, which favors formation of insoluble uric acid over soluble urate ion. Gastrointestinal bicarbonate loss due to chronic diarrhea leads to chronic metabolic acidosis and production of acidic urine, promoting formation of uric acid stones.

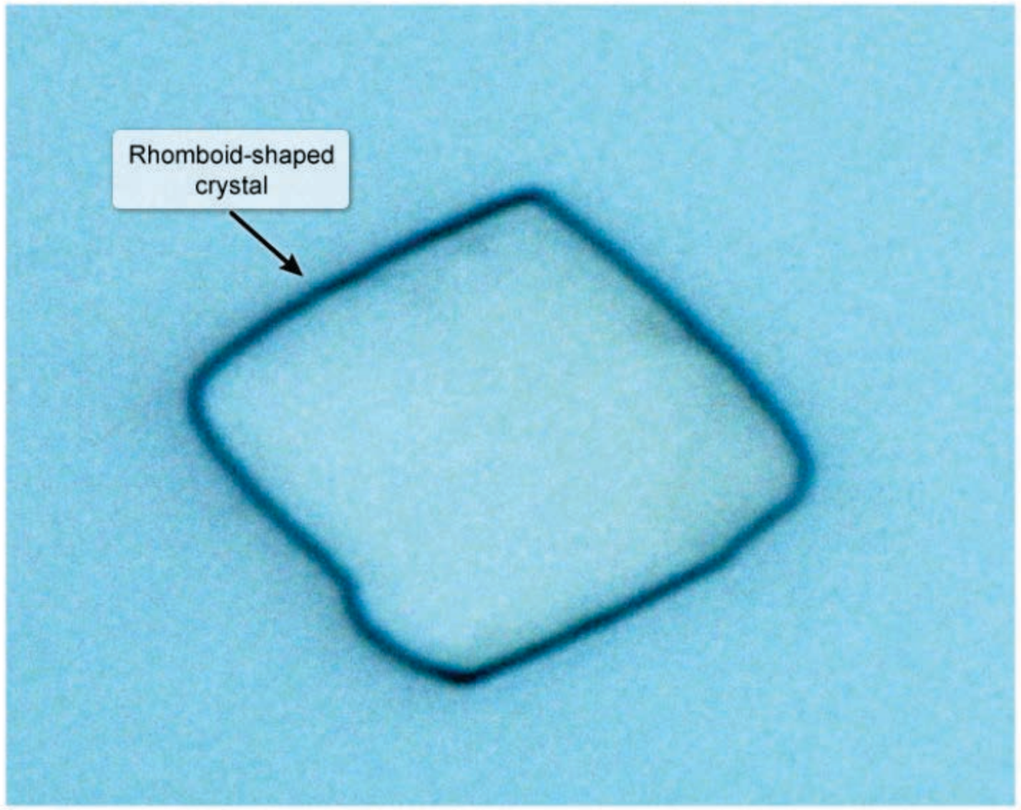
References

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- Supersaturation of urine with uric acid precipitates crystal formation

Exhibit Display

Uric acid crystals



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(Choice C) Overproduction of uric acid (eg, gout, myeloproliferative disorders) can lead to uric acid stones. However, this patient has no features of these disorders, and her stone formation is likely due to abnormally

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A 2-week-old boy is brought to the clinic by his parents for evaluation of his umbilicus. The parents report that since the umbilical cord stump separated 2 days ago, there has been drainage from the umbilicus that increases when the patient cries. He is exclusively breastfed and continues to have normal wet diapers and stool output. The patient was born at term, and the pregnancy and delivery were uncomplicated. Vital signs are normal. Physical examination of the abdomen shows clear to pale yellow fluid leaking from the umbilical stump site with mucosal tissue at the base of the umbilicus. Samples are obtained for complete blood count. Laboratory results are as follows:

Hemoglobin	14 g/dL
Platelets	240,000/mm^3
Leukocytes	11,000/mm^3
Neutrophils	60%
Lymphocytes	32%

Which of the following is the most likely cause of this patient's umbilical findings?

- A. Absence of neutrophil migration
- B. Duplication of the ureter
- C. Incomplete closure of anterior abdominal wall
- D. Patency of omphalomesenteric duct
- E. Persistence of allantois remnant

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Leukocytes	11,000/mm^3
Neutrophils	60%
Lymphocytes	32%

Which of the following is the most likely cause of this patient's umbilical findings?

✗ A. Absence of neutrophil migration (11%)

B. Duplication of the ureter (1%)

C. Incomplete closure of anterior abdominal wall (6%)

D. Patency of omphalomesenteric duct (17%)

✓ E. Persistence of allantois remnant (62%)

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Correct answer

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Explanation

Neonatal umbilical drainage		
Diagnosis	**Anatomy**	**Clinical findings**
Umbilical granuloma	• Excess granulation tissue • No communication with abdomen	• Serous umbilical moisture • Pedunculated mass
Patent urachus	• Connection between umbilicus & bladder	• Persistent leakage of urine
Patent omphalomesenteric duct	• Connection between umbilicus & bowel	• Persistent leakage of stool
Omphalitis	• Infection of umbilical cord stump	• Purulent drainage • Induration/erythema

Umbilical drainage in a neonate may be due to granulation tissue, infection, or congenital anomaly. In this case, the patient's persistent pale-yellow drainage (consistent with urine) is suggestive of a congenital urachal abnormality.

In utero, the caudal yolk sac normally forms a tubular outpouching called the **allantois**, which extends from the embryologic **bladder to the umbilicus**. As the bladder descends into the fetal pelvis, it stretches the allantois, which becomes thin and narrow. Epithelial proliferation obliterates the allantois lumen by 12 weeks gestation, forming a fibrous cord known as the **urachus**.

Failed obliteration of the allantois can lead to a **patent urachus**. This connection between the bladder and the umbilicus results in urinary umbilical drainage that increases with intraabdominal pressure (eg, **crying**, straining,

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Failed obliteration of the allantois can lead to a **patent urachus**. This connection between the bladder and the umbilicus results in urinary umbilical drainage that increases with intraabdominal pressure (eg, **crying**, straining, prone positioning). Partially failed obliteration can result in a range of defects, including a urachus that is open to the umbilicus (urachal sinus), open to the bladder (urachal diverticulum), or open only centrally (urachal cyst).

(Choice A) Leukocyte adhesion deficiency is characterized by impaired leukocyte migration due to defective adhesive molecules. Patients typically have leukocytosis and delayed (>1 month) umbilical cord stump separation, findings not present in this case.

(Choice B) A duplication of the renal collecting system (eg, 2 ureters originating from a single kidney) can result in aberrant insertion of a ureter into structures such as the urethra or epididymis. The umbilicus is not involved, so umbilical drainage does not occur.

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(Choice A) Leukocyte adhesion deficiency is characterized by impaired leukocyte migration due to defective adhesive molecules. Patients typically have leukocytosis and delayed (>1 month) umbilical cord stump separation, findings not present in this case.

(Choice B) A duplication of the renal collecting system (eg, 2 ureters originating from a single kidney) can result in aberrant insertion of a ureter into structures such as the urethra or epididymis. The umbilicus is not involved, so umbilical drainage does not occur.

(Choice C) Incomplete closure of the anterior abdominal wall describes gastroschisis, in which viscera protrude through an abdominal wall defect adjacent to the umbilicus. Isolated umbilical drainage is not consistent with this diagnosis.

(Choice D) The omphalomesenteric (or vitelline) duct is a diverticulum of the yolk sac that extends from the embryologic midgut to the umbilicus; it normally involutes in early gestation. Persistent patency connects the bowel to the umbilicus, and patients may exhibit fecal (not urinary) umbilical discharge.

Educational objective:
The urachus is a remnant of the allantois that extends from the bladder to the umbilicus. Failed obliteration of the allantois lumen can result in a patent urachus, which presents with urinary drainage from the umbilicus in the neonate.

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the patient's persistent pale-yellow drainage (consistent with urine) is suggestive of a congenital urachal abnormality.

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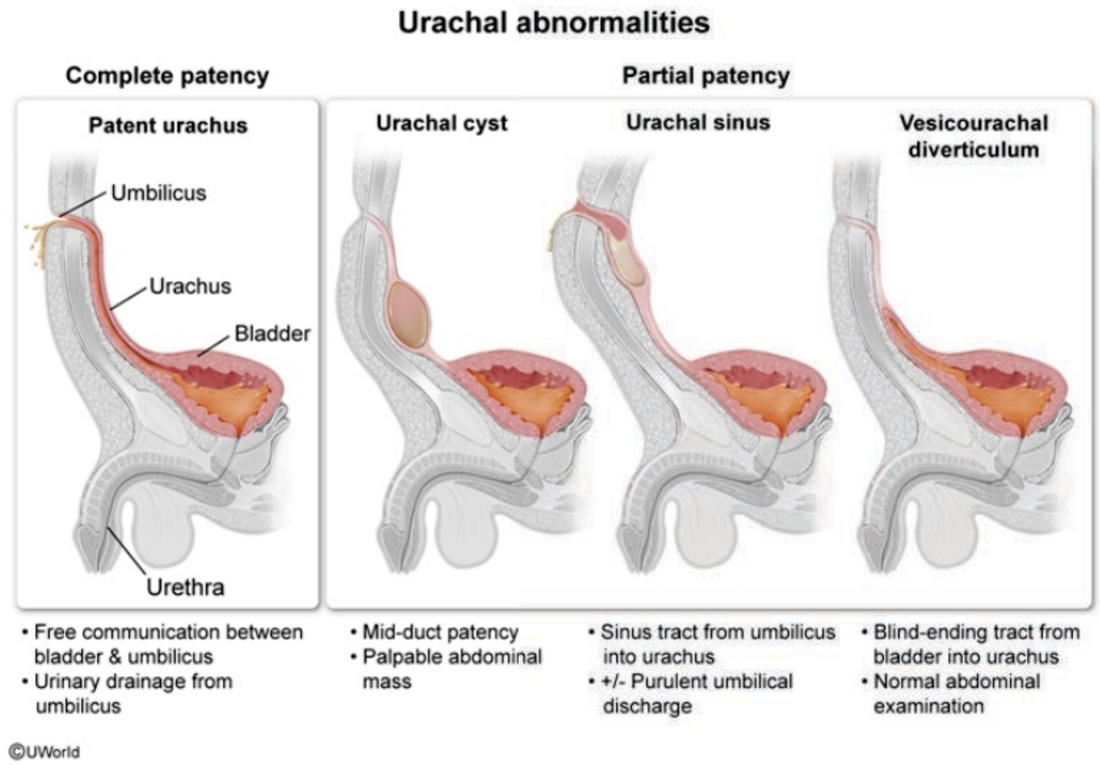
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Educational objective:

The urachus is a remnant of the allantois that extends from the bladder to the umbilicus. Failed obliteration of the

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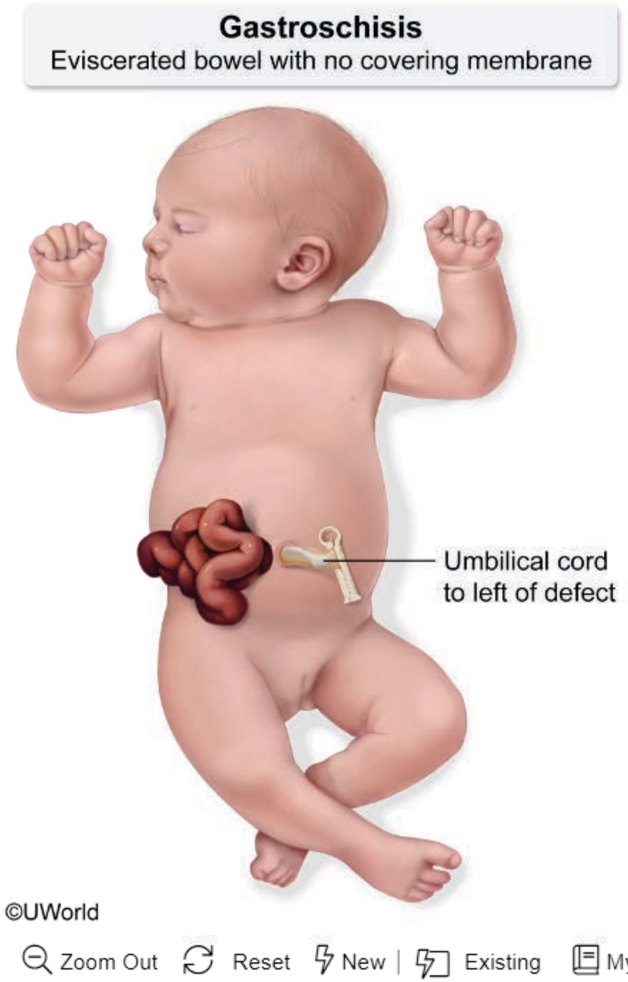
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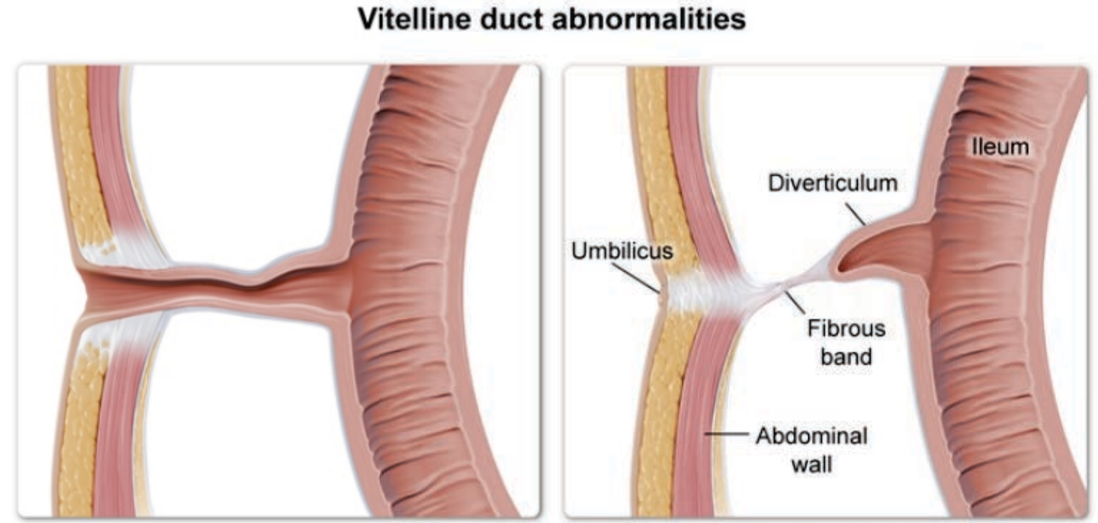
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A 7-year-old boy is brought to the office due to swelling of the hands and feet. Two weeks ago, the patient was treated for anaphylaxis following a bee sting. During the past 10 days, he has had progressive hand and foot swelling, and his pants feel tighter than usual. The patient's urine has also become frothy. Examination shows periorbital edema and pitting edema of the hands and feet, as well as mild ascites. Lungs are clear to auscultation. Urinalysis results are as follows:

Protein	+4
Blood	negative
Glucose	negative
Ketones	negative
White blood cells	1-2/hpf
Red blood cells	1-2/hpf
Casts	hyaline casts

Biopsy of this patient's kidneys would most likely show which of the following microscopy findings?

	Light microscopy	Immunofluorescence	Electron microscopy
A.	Cellular proliferation in segmental areas	Globular deposits of IgA	Mesangial deposits
B.	Cellular proliferation with increased neutrophils in	Granular deposits of complement and IgG	Subepithelial deposits

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B.	Cellular proliferation with increased neutrophils in capillaries	Granular deposits of complement and IgG	Subepithelial deposits
C.	Crescent formation	Linear deposits of IgG	Negative for deposits
D.	Diffuse thickening of glomerular basement membrane	Granular deposits of complement and IgG	Subepithelial deposits
E.	Normal histology	Negative for complement and IgG	Effacement of podocytes

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Casts	hyaline casts

Biopsy of this patient's kidneys would most likely show which of the following microscopy findings?

	Light microscopy	Immunofluorescence	Electron microscopy	
A.	Cellular proliferation in segmental areas	Globular deposits of IgA	Mesangial deposits	(5%)
B.	Cellular proliferation with increased neutrophils in capillaries	Granular deposits of complement and IgG	Subepithelial deposits	(4%)
✗ C.	Crescent formation	Linear deposits of IgG	Negative for deposits	(1%)
D.	Diffuse thickening of glomerular basement membrane	Granular deposits of complement and IgG	Subepithelial deposits	(6%)
✓ E.	Normal histology	Negative for complement and IgG	Effacement of podocytes	(81%)

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Correct answer
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Answered correctly

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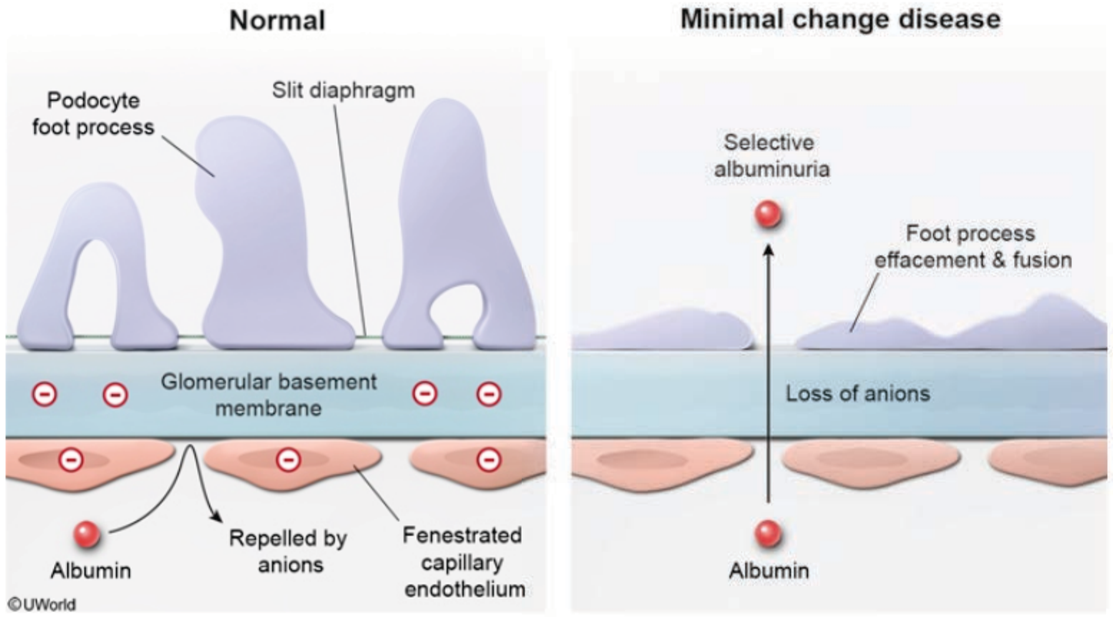
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charge results in the selective loss of albumin in the urine, which causes hypoalbuminemia and edema.

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This pediatric patient developed **nephrotic syndrome** (ie, generalized edema, hyperlipidemia, hypoalbuminemia, massive proteinuria with resultant "frothy" urine) after a bee sting. This presentation suggests **minimal change disease** (MCD), the most common cause of nephrotic syndrome in **young children**. MCD is often idiopathic but can occur after an inciting event, including respiratory infections, immunizations, or insect sting/bite. Subsequent T-cell dysfunction leads to the production of a glomerular permeability factor (possibly IL-13) which damages podocytes and decreases the anionic properties of the glomerular basement membrane (GBM). Loss of negative charge results in the selective loss of albumin in the urine, which causes hypoalbuminemia and edema.

Most children with MCD can be diagnosed presumptively based on clinical presentation, and renal biopsy is usually unnecessary. If biopsy is performed, light microscopy (LM) shows **normal glomeruli**, and **no immunoglobulin** or complement deposits are seen with immunofluorescent staining. However, electron microscopy (EM) shows diffuse **podocyte foot process effacement** and fusion. These abnormal findings are generally reversible after corticosteroid therapy, and most children experience rapid resolution with an excellent long-term prognosis.

(Choice A) IgA nephropathy presents with nephritic syndrome; patients typically develop marked hematuria with red blood cell casts on urinalysis. Deposits of IgA are noted in the mesangium on EM and immunofluorescence microscopy (IF), whereas LM demonstrates resultant glomerular hypercellularity in affected segments.

(Choice B) Poststreptococcal glomerulonephritis is a nephritic syndrome that typically occurs 2-4 weeks after infection with group A Streptococcus. LM demonstrates hypercellular glomeruli, whereas IF shows a "lumpy-bumpy" pattern of granular IgG and C3 deposition on the GBM. EM also demonstrates subepithelial immune complex deposits.

(Choice C) Antiglomerular basement membrane disease causes a linear deposition of IgG and C3 on the GBM; it typically results in a crescentic glomerulonephritis (eg, nephritic syndrome; hematuria, red blood cell casts) visible on LM. EM demonstrates breakage of the GBM, but immune complex deposits are absent.

(Choice D) Membranous nephropathy causes a nephrotic syndrome but is rarer in children; it is often associated

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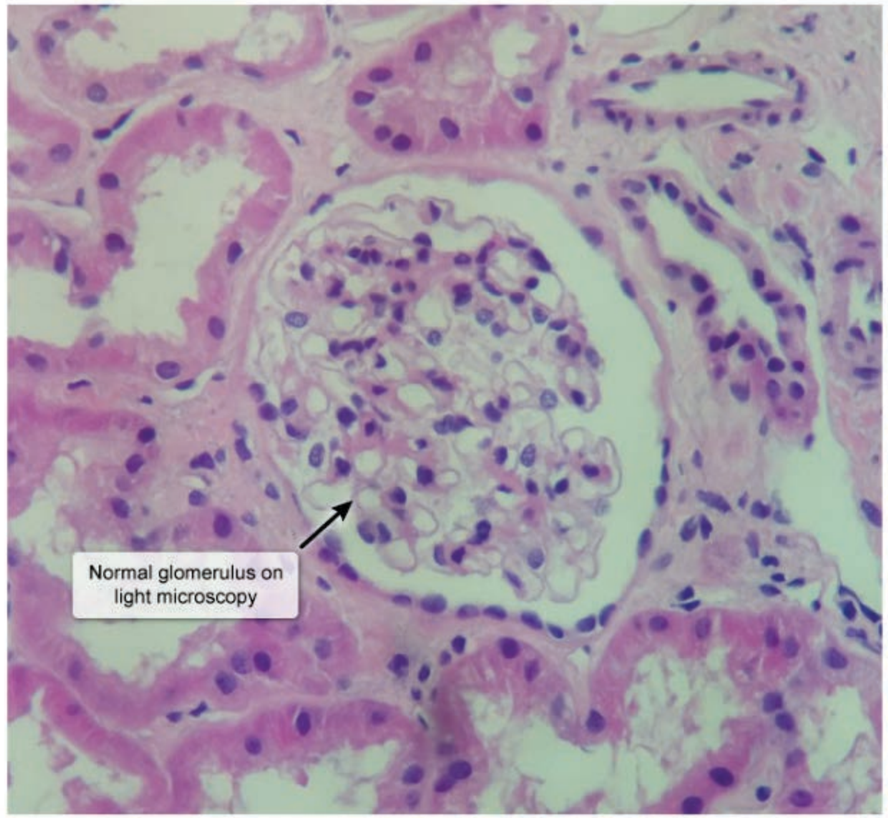
(Choice D) Membranous nephropathy causes a nephrotic syndrome but is rarer in children; it is often associated with viral hepatitis, solid tumors, or lupus. LM reveals diffuse GBM thickening, which is due to the granular deposition of immune complexes (IgG and C3); EM demonstrates subepithelial deposits.

Educational objective:
Minimal change disease is the most common cause of nephrotic syndrome in children. Classic manifestations include proteinuria, hypoalbuminemia, and edema that are usually reversible with corticosteroids. The principal lesion is a diffuse foot process effacement that can be seen on electron microscopy. Light and immunofluorescence microscopy are normal.

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Minimal change disease



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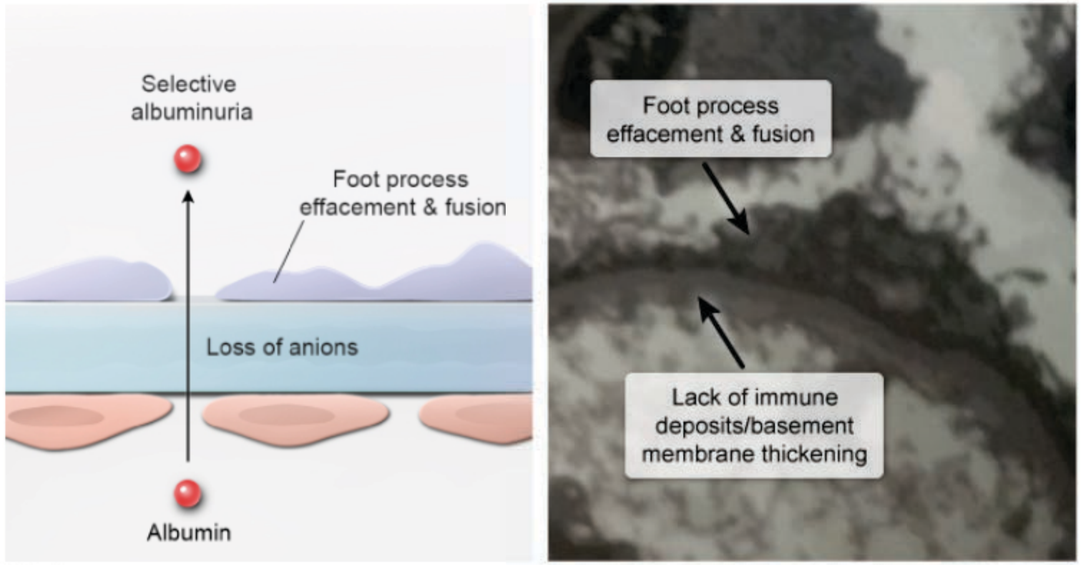
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(Choice B) Poststreptococcal glomerulonephritis is a nephritic syndrome that typically occurs 2-4 weeks after

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Minimal change disease



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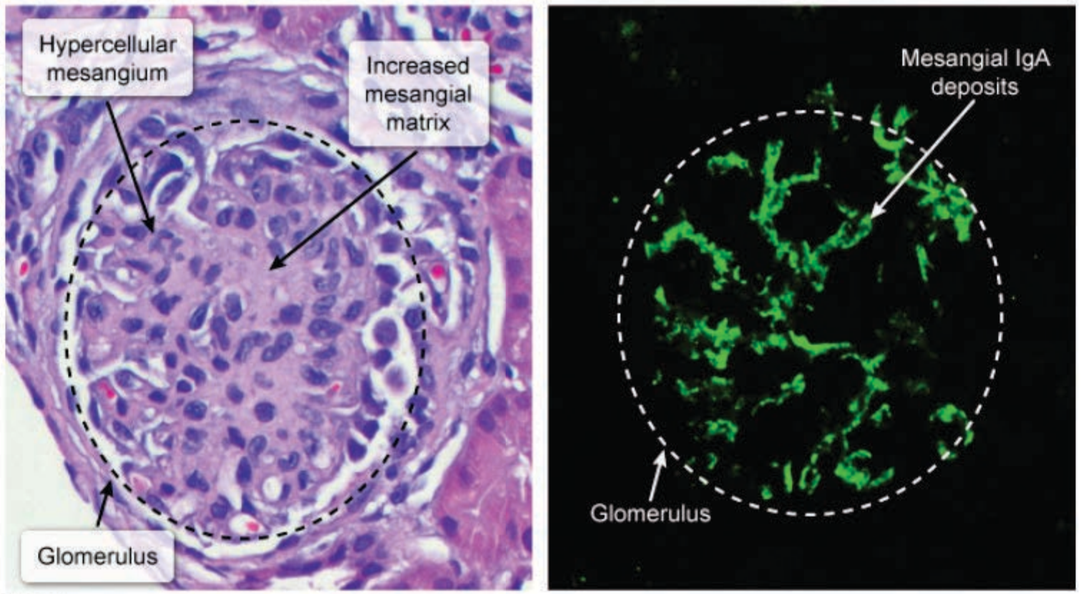
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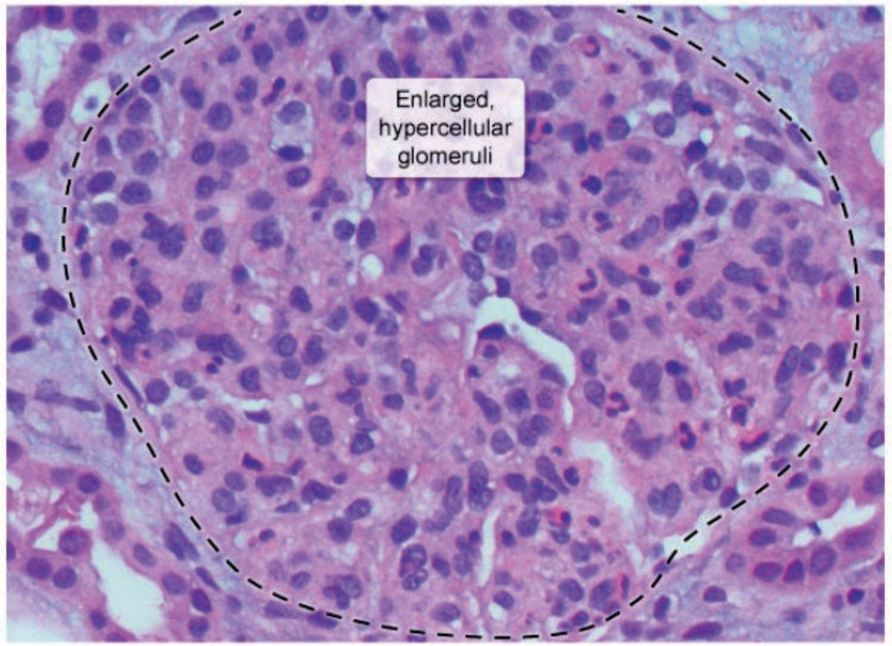
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Acute postinfectious glomerulonephritis



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massive proteinuria with resultant "frothy" urine) after a bee sting. This presentation suggests **minimal change disease** (MCD), the most common cause of nephrotic syndrome in **young children**. MCD is often idiopathic but can

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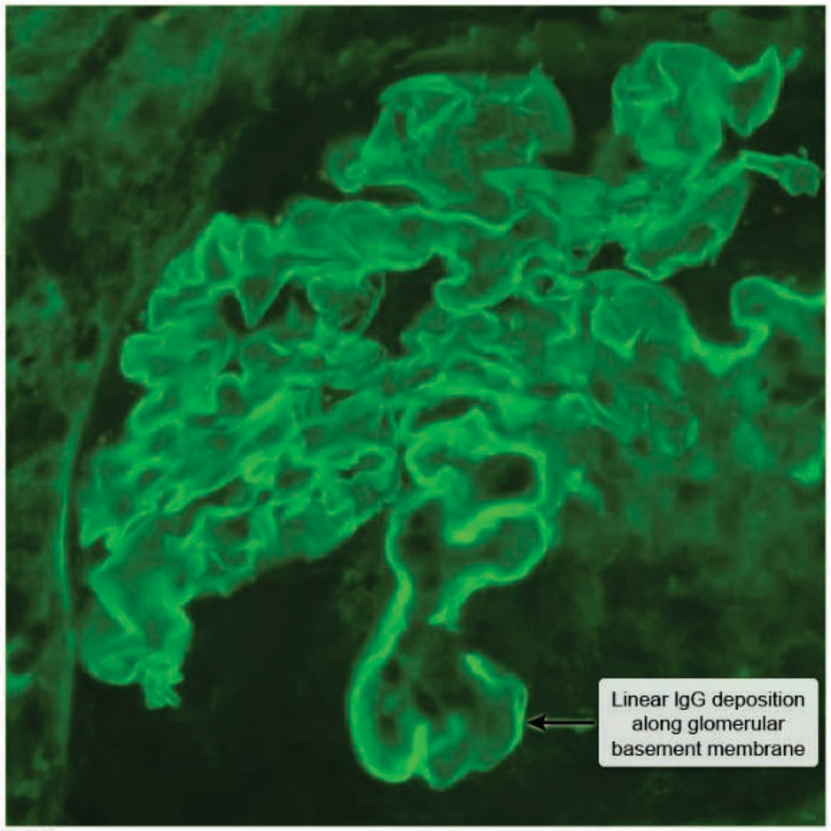
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with viral hepatitis, solid tumors, or lupus. LM reveals diffuse GBM thickening, which is due to the granular deposition of immune complexes (IgG and C3); EM demonstrates subepithelial deposits.

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Anti-glomerular basement membrane disease



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massive proteinuria with resultant "frothy" urine) after a bee sting. This presentation suggests **minimal change disease** (MCD), the most common cause of nephrotic syndrome in **young children**. MCD is often idiopathic but can

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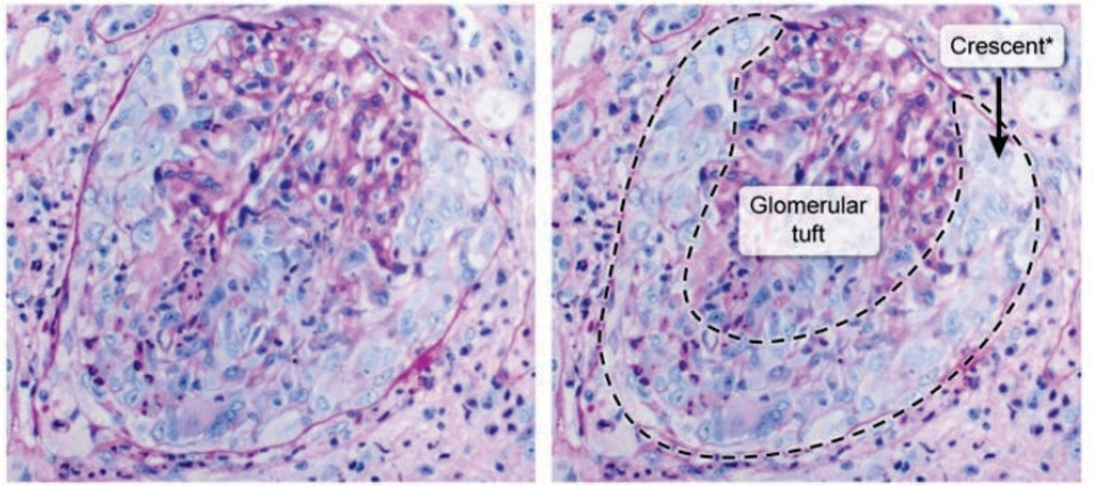
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Crescentic glomerulonephritis



*Proliferating epithelial cells and infiltrating macrophages

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podocytes and decreases the anionic properties of the glomerular basement membrane (GBM). Loss of negative

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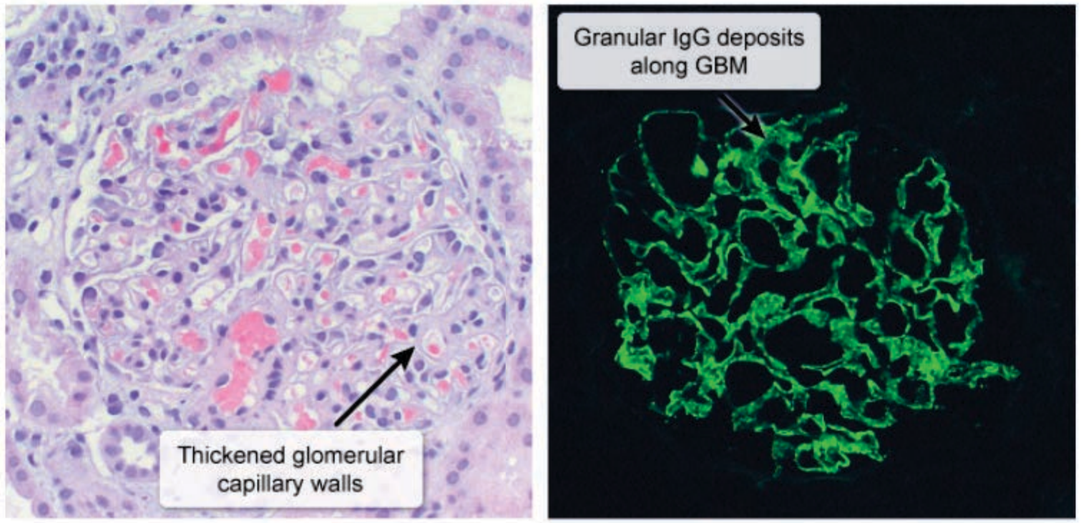
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Minimal change disease is the most common cause of nephrotic syndrome in children. Classic manifestations

Membranous nephropathy



Hematoxylin & eosin stain

Immunofluorescence

GBM = glomerular basement membrane.

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A 46-year-old woman is hospitalized for recurrent renal colic. She has passed 2 urinary stones during the last 2 years. The most recent stone contained 80% calcium phosphate and 20% calcium oxalate. The patient also has diffuse aches and pains and has a history of peptic ulcer disease, for which she takes famotidine daily. Laboratory results are as follows:

Serum sodium	140 mEq/L
Serum potassium	4.0 mEq/L
Serum chloride	103 mEq/L
Serum creatinine	0.8 mg/dL
Serum calcium	12.0 mg/dL
Serum phosphorus	2.4 mg/dL
24-hour urinary calcium excretion	350 mg (normal: 100-300)

Which of the following changes in bone structure is most likely associated with this patient's condition?

- A. Lamellar bone structure resembling a mosaic pattern
- B. Osteoid matrix accumulation around trabeculae
- C. Spongiosa filling medullary canals with no mature trabeculae
- D. Subperiosteal resorption with cortical thinning
- E. Trabecular thinning with fewer interconnections

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24-hour urinary calcium excretion	350 mg (normal: 100-300)

Which of the following changes in bone structure is most likely associated with this patient's condition?

- ✗ A. Lamellar bone structure resembling a mosaic pattern (8%)
- B. Osteoid matrix accumulation around trabeculae (6%)
- C. Spongiosa filling medullary canals with no mature trabeculae (5%)
- ✓ D. Subperiosteal resorption with cortical thinning (61%)
- E. Trabecular thinning with fewer interconnections (17%)

Incorrect
Correct answer
D

61%
Answered correctly

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This patient with recurrent calcium nephrolithiasis and hypercalcemia most likely has **primary hyperparathyroidism** (PHPT). Besides kidney stones, classic manifestations include bone pain, gastrointestinal disturbances (eg, peptic ulcer disease), and psychiatric symptoms (ie, "bones, stones, abdominal groans, and psychologic moans"). However, asymptomatic hypercalcemia is the most common presentation. 85% of cases are caused by a parathyroid adenoma, but PHPT can also be due to parathyroid hyperplasia or, rarely, parathyroid cancer.

Excess parathyroid hormone causes **hypercalcemia** via the following mechanisms:

- Increased renal tubular Ca^{2+} reabsorption (although most patients have net **hypercalciuria** due to the increased filtered calcium load)
- Increased renal production of 1,25-dihydroxyvitamin D (which in turn increases gastrointestinal Ca^{2+} absorption)
- Increased bone resorption (via osteoclast activation)

Patients usually also have **hypophosphatemia** due to decreased phosphate reabsorption in the proximal renal tubules.

Because of the increased bone resorption, PHPT often leads to **osteoporosis**. However, unlike the typical osteoporosis of aging, which predominantly affects trabecular bone, osteoporosis in PHPT is most pronounced in the **cortical (compact) bone** of the appendicular skeleton (eg, pectoral girdle, pelvic girdle, limbs). Cortical thinning is characteristic and appears radiologically as **subperiosteal erosions**. More advanced disease can present as osteitis fibrosa cystica, characterized by granular decalcification of the skull ("salt-and-pepper skull"), osteolytic cysts, and brown tumors.

(Choice A) Disorganized lamellar bone in a mosaic pattern is a characteristic finding in Paget disease of bone. Serum calcium and phosphorus are normal in these patients.

(Choice B) Osteoid matrix accumulation around trabeculae is seen in vitamin D deficiency. Histologically, there is

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Patients usually also have **hypophosphatemia** due to decreased phosphate reabsorption in the proximal renal tubules.

Because of the increased bone resorption, PHPT often leads to **osteoporosis**. However, unlike the typical osteoporosis of aging, which predominantly affects trabecular bone, osteoporosis in PHPT is most pronounced in the **cortical (compact) bone** of the appendicular skeleton (eg, pectoral girdle, pelvic girdle, limbs). Cortical thinning is characteristic and appears radiologically as **subperiosteal erosions**. More advanced disease can present as osteitis fibrosa cystica, characterized by granular decalcification of the skull ("salt-and-pepper skull"), osteolytic cysts, and brown tumors.

(Choice A) Disorganized lamellar bone in a mosaic pattern is a characteristic finding in Paget disease of bone. Serum calcium and phosphorus are normal in these patients.

(Choice B) Osteoid matrix accumulation around trabeculae is seen in vitamin D deficiency. Histologically, there is excessive unmineralized osteoid with widened osteoid seams. Patients typically have low urinary calcium.

(Choice C) Osteopetrosis ("marble bone disease") is characterized by persistence of the primary spongiosa in the medullary cavity with no mature trabeculae. It is caused by decreased osteoclastic bone resorption, resulting in accumulation of woven bone and diffuse skeletal thickening.

(Choice E) Trabecular thinning with fewer interconnections is characteristic of postmenopausal osteoporosis. Although long-standing PHPT causes thinning of cortical bone, the trabecular architecture remains relatively preserved.

Educational objective:
Increased bone resorption in primary hyperparathyroidism leads to osteoporosis primarily involving the cortical bone of the appendicular skeleton. The cortical thinning appears radiologically as subperiosteal erosions. More advanced disease can present as osteitis fibrosa cystica (ie, granular decalcification of the skull, osteolytic cysts, and brown tumors).

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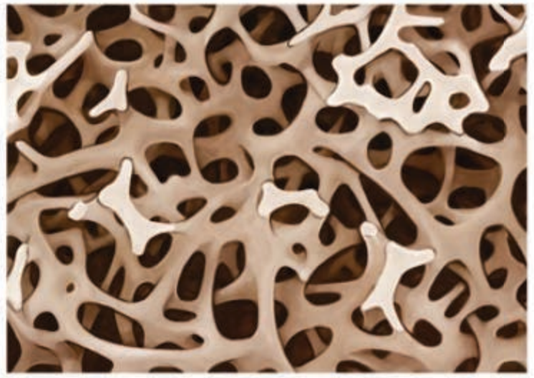
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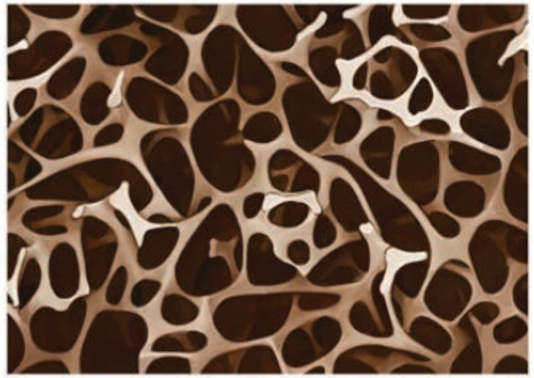
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Exhibit Display

Normal trabecular bone



Osteoporotic bone



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Patho

Subject | System | Topic

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A 7-year-old boy is brought to the emergency department by his parents for arthralgias. He had a cough and runny nose last week but otherwise has been in good health. Temperature is 37 C (98.6 F), blood pressure is 95/65 mm Hg, pulse is 92/min, and respirations are 20/min. Physical examination shows raised, red-purple papules, some of which have coalesced, over the patient's buttocks and thighs. Auscultation of the lungs and heart is normal. The abdomen is soft with normal bowel sounds. The knees are tender but do not appear warm or swollen. Urinalysis results are as follows:

Protein	2+
Blood	moderate
Leukocyte esterase	trace
Nitrites	negative
White blood cells	1-2/hpf
Red blood cells (RBCs)	many/hpf
Casts	RBC casts

Which of the following mechanisms is the most likely underlying cause of this patient's renal findings?

- A. Autoantibodies against podocyte antigens
- B. Autoantibodies to host cell basement membranes
- C. Immune complex deposition in glomerular mesangium
- D. Thrombosis of glomerular capillaries
- E. T-lymphocyte cytotoxicity against virally-infected mesangial cells

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nose last week but otherwise has been in good health. Temperature is 37 C (98.6 F), blood pressure is 95/65 mm Hg, pulse is 92/min, and respirations are 20/min. Physical examination shows raised, red-purple papules, some of which have coalesced, over the patient's buttocks and thighs. Auscultation of the lungs and heart is normal. The abdomen is soft with normal bowel sounds. The knees are tender but do not appear warm or swollen. Urinalysis results are as follows:

Protein	2+
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Nitrites	negative
White blood cells	1-2/hpf
Red blood cells (RBCs)	many/hpf
Casts	RBC casts

Which of the following mechanisms is the most likely underlying cause of this patient's renal findings?

- A. Autoantibodies against podocyte antigens (6%)
- ✗ B. Autoantibodies to host cell basement membranes (10%)
- ✓ C. Immune complex deposition in glomerular mesangium (74%)
- D. Thrombosis of glomerular capillaries (4%)
- E. T-lymphocyte cytotoxicity against virally-infected mesangial cells (4%)

Incorrect
Correct answer
C

74%
Answered correctly

40 secs
Time Spent

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Explanation

IgA vasculitis (Henoch-Schönlein purpura)	
Pathogenesis	• Deposition of IgA immune complexes in small vessels activates complement • Neutrophilic inflammation & vascular damage • Often follows an upper respiratory infection
Clinical manifestations	• Palpable purpura/petechiae on the lower extremities • Arthritis/arthralgia • Abdominal pain, gastrointestinal bleeding, intussusception • Renal disease (hematuria ± proteinuria)
Diagnosis	• Usually clinical • Skin biopsy: leukocytoclastic vasculitis, IgA deposition in vessel walls

This patient has findings consistent with Henoch-Schönlein purpura (HSP) (ie, IgA vasculitis), a leukocytoclastic vasculitis most common in school-aged children and characterized by lower extremity palpable purpura, arthralgia/arthritis, abdominal pain, and/or renal abnormalities. HSP is caused by the deposition of **IgA immune complexes** in small-vessel walls and may be precipitated by an upper respiratory tract infection, as seen in this patient.

HSP renal disease is an immune-mediated glomerulonephritis with microscopic features identical to IgA nephropathy:

- **Mesangial deposition** of IgA immune complexes triggers **mesangial cell proliferation** and extracellular matrix deposition, primarily via enhanced expression of platelet-derived growth factor and transforming growth factor beta.
- IgA Immune complexes also trigger **complement activation** via the alternative and lectin pathways;

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manifestations	• Abdominal pain, gastrointestinal bleeding, intussusception • Renal disease (hematuria ± proteinuria)
Diagnosis	• Usually clinical • Skin biopsy: leukocytoclastic vasculitis, IgA deposition in vessel walls

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- **Mesangial deposition** of IgA immune complexes triggers **mesangial cell proliferation** and extracellular matrix deposition, primarily via enhanced expression of platelet-derived growth factor and transforming growth factor beta.
- IgA Immune complexes also trigger **complement activation** via the alternative and lectin pathways; hydrolyzed complement proteins (eg, c5a) act as chemokines that attract **neutrophils**, which produce oxidants and release proteases (eg, elastase) that are damaging to glomerular capillaries.
- Macrophages may also be recruited to the glomerulus, where they cause further damage to glomerular capillaries, promote **fibrin deposition**, and contribute to **crescent formation** in severe cases.

Most children with HSP-related renal disease have mild nephritis characterized by **hematuria**, red blood cell (RBC) casts, non–nephrotic range proteinuria, and a normal creatinine. However, severe complications (eg, nephrotic syndrome, acute kidney injury) can occur.

(Choice A) IgG autoantibodies to phospholipase A$_2$ receptor on podocytes can lead to subepithelial immune

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- Macrophages may also be recruited to the glomerulus, where they cause further damage to glomerular capillaries, promote **fibrin deposition**, and contribute to **crescent formation** in severe cases.

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(Choice A) IgG autoantibodies to phospholipase A_2 receptor on podocytes can lead to subepithelial immune deposition and membranous nephropathy. Patients have nephrotic syndrome (eg, edema, marked proteinuria [usually ≥3+]), not hematuria.

(Choice B) Anti-glomerular basement membrane disease is caused by an autoantibody to the alpha 3 chain of type IV collagen and is often associated with pulmonary hemorrhage. Although patients have nephritic syndrome with hematuria and RBC casts, arthralgias and purpura are not seen.

(Choice D) Prothrombotic conditions (eg, antiphospholipid syndrome) can cause thrombosis of the glomerular capillaries, and urinalysis may show hematuria and/or proteinuria. Although purpura may occur due to consumptive thrombocytopenia, the lesions would be diffuse, not localized to the lower extremities (immune complex vasculitis tends to affect dependent areas of the skin). In addition, his recent upper respiratory tract infection is more characteristic of HSP.

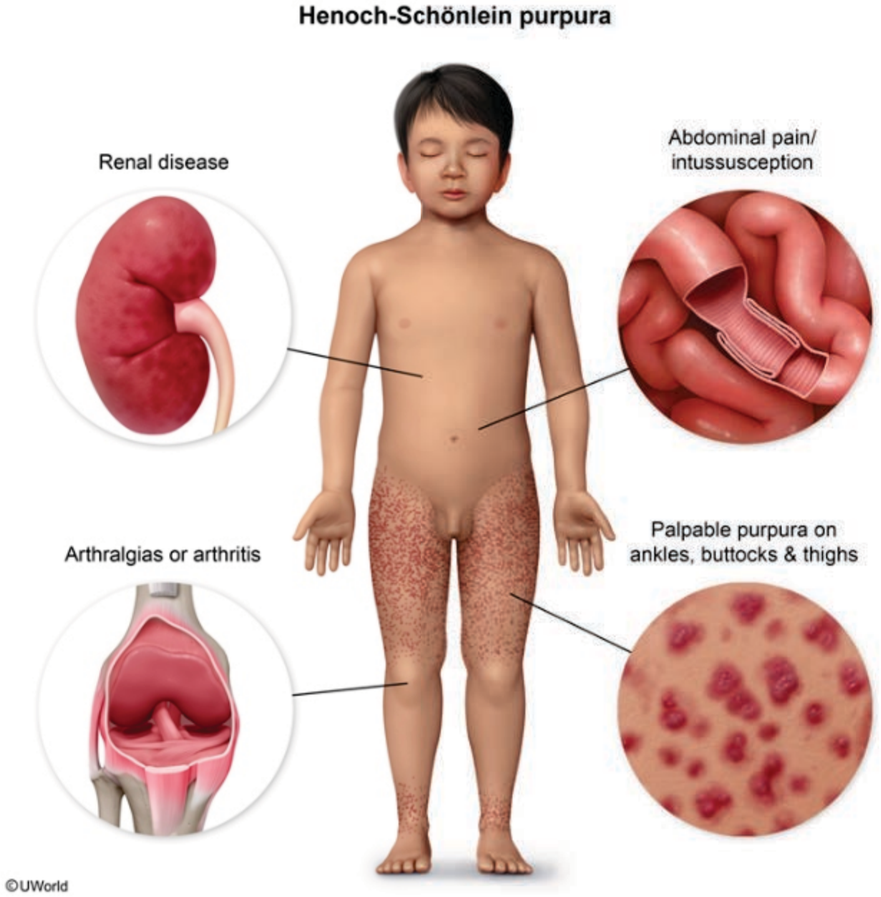
(Choice E) In rapidly progressive glomerulonephritis, activated T lymphocytes secrete cytokines that stimulate macrophage activity, a process that contributes to crescent formation. However, T lymphocyte-mediated cytotoxicity is not a mechanism of glomerular injury in HSP.

Educational objective:
Henoch-Schönlein purpura is an IgA-mediated, leukocytoclastic vasculitis that presents with palpable purpura, arthralgia/arthritis, abdominal pain, and/or hematuria. Renal involvement is due to mesangial deposition of IgA immune complexes with subsequent mesangial cell proliferation, neutrophilic infiltration, and glomerular damage.

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- Palpable purpura/petechiae on the lower extremities

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Most children with HSP-related renal disease have mild nephritis characterized by **hematuria**, red blood cell (RBC) casts, non–nephrotic range proteinuria, and a normal creatinine. However, severe complications (eg, nephrotic

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- Palpable purpura/petechiae on the lower extremities

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Henoch-Schönlein purpura



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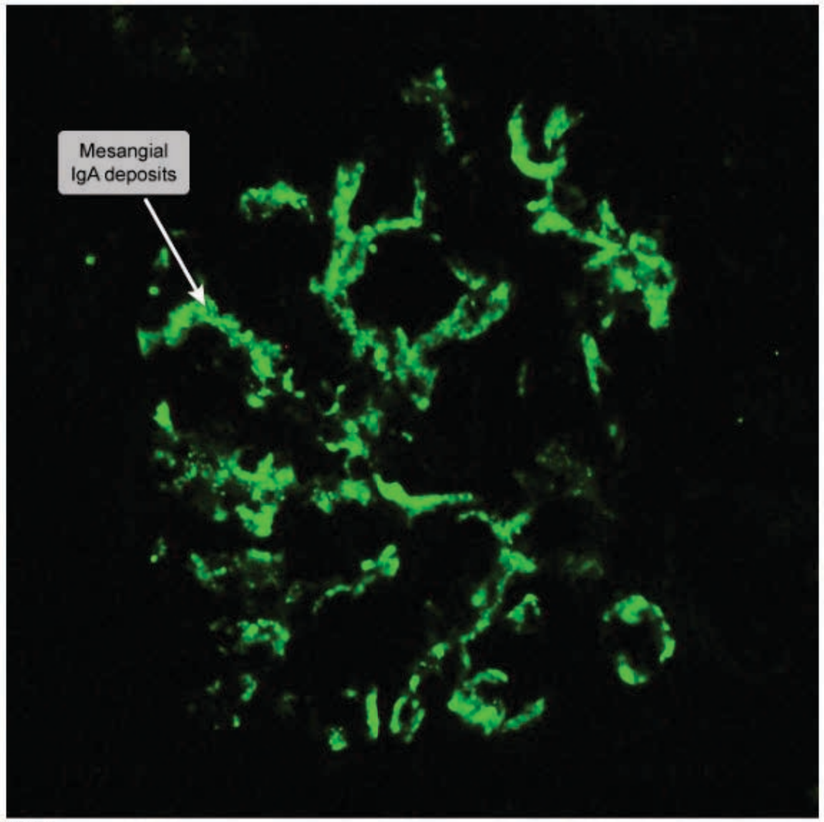
Most children with HSP-related renal disease have mild nephritis characterized by **hematuria**, red blood cell (RBC) casts, non–nephrotic range proteinuria, and a normal creatinine. However, severe complications (eg, nephrotic

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- Palpable purpura/petechiae on the lower extremities

Exhibit Display

IgA nephropathy



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Most children with HSP-related renal disease have mild nephritis characterized by **hematuria**, red blood cell (RBC) casts, non–nephrotic range proteinuria, and a normal creatinine. However, severe complications (eg, nephrotic

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A 46-year-old woman being evaluated for irregular vaginal bleeding is found to have invasive cervical carcinoma. She undergoes total abdominal hysterectomy and bilateral salpingo-oophorectomy. Pelvic lymphadenectomy was also performed, during which several enlarged nodes around the pelvic vessels were resected. A week after the surgery, the patient begins to experience left-sided flank pain that radiates to the groin. Her temperature is 36.1 C (97 F), blood pressure is 120/70 mm Hg, and pulse is 84/min. On physical examination, there is a ballotable left flank mass. Which of the following most likely accounts for this physical examination finding?

- A. Hydronephrosis
- B. Interstitial nephritis
- C. Renal cell carcinoma
- D. Renal cystic disease
- E. Renal vein thrombosis
- F. Vesicoureteral reflux

Submit

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- ✓ A. Hydronephrosis (71%)
- ✗ B. Interstitial nephritis (1%)
- C. Renal cell carcinoma (6%)
- D. Renal cystic disease (2%)
- E. Renal vein thrombosis (11%)
- F. Vesicoureteral reflux (6%)

Incorrect
Correct answer
A

71%
Answered correctly

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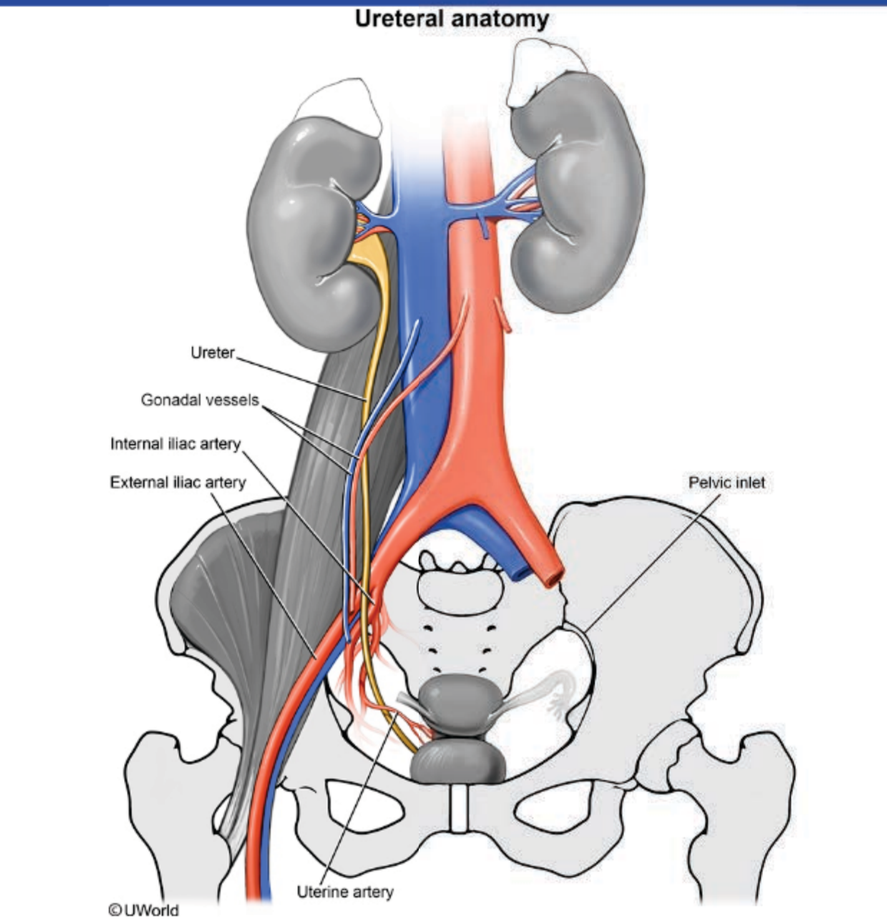
Explanation



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flank mass. Which of the following most likely accounts for this physical examination finding?

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Flank pain radiating to the groin with a ballotable (ie, palpatable between both hands) flank mass that develops within a week of pelvic surgery suggests **ureteric obstruction**. The ureter runs in close proximity to the pelvic vessels. It courses anterior to the iliac vessels (area of resection of the pelvic nodes, which drain the uterus and cervix) and just posterior to the uterine artery near the lateral fornix of the vagina. It is vulnerable to injury during **pelvic surgery**, such as that involved in hysterectomy with pelvic lymphadenectomy. Unintentional ureteral ligation causes obstruction with **hydronephrosis** and flank pain due to distension of the ureter and renal pelvis. Urine output and serum creatinine remain within normal limits in most individuals with unilateral obstruction because the contralateral kidney functions normally and compensates for decreased functioning of the affected kidney.

(Choice B) Acute interstitial nephritis is classically medication induced. Signs and symptoms include fever, transient rash, and acute renal failure.

(Choices C and D) Renal cell carcinoma classically causes hematuria, flank pain, and a palpable mass. Adult polycystic kidney disease is an autosomal dominant condition characterized by multiple renal, pancreatic, and hepatic cysts. This patient had no evidence of a renal mass prior to surgery, and these conditions would not develop over a period of a week.

(Choice E) Postsurgical patients are at increased risk for deep venous thrombosis, mostly in the lower extremities or pulmonary vasculature. Renal vein thrombosis is unusual postoperatively but may be seen in patients with nephrotic syndrome.

(Choice F) Vesicoureteral reflux can be a complication of prostatectomy or bladder surgery. It predisposes to pyelonephritis and hydroureteronephrosis.

Educational objective:
The ureters run in close proximity to the pelvic lymph nodes and the uterine artery in the female pelvis, which predisposes them to injury during pelvic surgery.

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A 60-year-old man comes to the office due to persistent cough for the past several weeks. He reports producing minimal sputum that recently has contained occasional specks of blood. The patient also has anorexia and has lost 7 kg (15.4 lb) over the past 2 months. He has no previous medical conditions and takes no medications. The patient has smoked a pack of cigarettes daily for 40 years and drinks alcohol on social occasions. Temperature is 37.1 C (98.7 F), blood pressure is 130/80 mm Hg, pulse is 72/min, and respirations are 16/min. On physical examination, respirations are unlabored, and there are occasional wheezes on the left side. The remainder of the examination shows no abnormalities. A chest x-ray reveals a hilar mass with adenopathy on the left side. Laboratory results demonstrate a decreased serum sodium level. Which of the following additional laboratory abnormalities are most likely to be present in this patient?

	Serum osmolality	Urine osmolality	Urine sodium
○ A.	High	High	Normal
○ B.	High	Low	Normal
○ C.	Low	High	High
○ D.	Low	High	Low
○ E.	Low	Low	Low

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		Serum osmolality	Urine osmolality	Urine sodium	
✗	A.	High	High	Normal	(0%)
	B.	High	Low	Normal	(3%)
✓	C.	Low	High	High	(69%)
	D.	Low	High	Low	(22%)
	E.	Low	Low	Low	(3%)

Incorrect
Correct answer
C

69%
Answered correctly

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Time Spent

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Explanation

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Explanation

Conditions associated with abnormal sodium levels			
Disorder	**Serum sodium**	**Serum osmolality**	**Urine osmolality**
Diabetes insipidus	High/normal	High	Low
Primary polydipsia	Low	Low	Low
Diabetes mellitus*	Low	High	High
SIADH	Low	Low	High

*In the setting of marked hyperglycemia.

SIADH = syndrome of inappropriate secretion of antidiuretic hormone.

This patient with a significant smoking history, cough, weight loss, and left-sided **hilar lung mass** with adenopathy likely has lung cancer. He also has new **hyponatremia**. Certain tumors (eg, small cell lung carcinoma, head and neck cancer) can ectopically produce antidiuretic hormone (ADH), which can lead to hyponatremia due to the **syndrome of inappropriate secretion of ADH** (SIADH).

ADH secretion from the posterior pituitary is normally stimulated by high serum osmolality (eg, water deprivation) or low extracellular volume (eg, dehydration). Increased ADH leads to water reabsorption in the renal collecting ducts, lowering serum osmolality and suppressing further ADH secretion. However, in SIADH, excessive uncontrolled ADH secretion occurs, causing the following changes:

- **Hyponatremia** and **low serum osmolality** as a result of excess water retention
- **Concentrated urine** with **high urine osmolality** as a result of impaired renal water excretion
- **High urine sodium** caused by increased secretion of natriuretic peptides (eg, brain natriuretic peptides)

(Choice D)

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Primary polydipsia	Low	Low	Low
Diabetes mellitus*	Low	High	High
SIADH	Low	Low	High

*In the setting of marked hyperglycemia.
SIADH = syndrome of inappropriate secretion of antidiuretic hormone.

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- **High urine sodium** caused by increased secretion of natriuretic peptides (eg, brain natriuretic peptides) **(Choice D)**

Patients with SIADH are typically **euvolemic** (eg, absent jugular venous distension, normotension). Initially, increased reabsorption of water in SIADH may cause a transient volume expansion; however, subsequent natriuresis (sodium and water excretion) restores the extracellular volume to normal.

(Choice A) High serum osmolality and high urine osmolality (concentrated urine) can be seen in severe hyperglycemia (eg, diabetic ketoacidosis). High urine osmolality and polyuria results from increased glucose excretion in the urine (osmotic diuresis); dilutional hyponatremia can also occur due to the glucose-driven osmotic

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- **Hyponatremia** and **low serum osmolality** as a result of excess water retention
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(Choice D)

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(Choice A) High serum osmolality and high urine osmolality (concentrated urine) can be seen in severe hyperglycemia (eg, diabetic ketoacidosis). High urine osmolality and polyuria results from increased glucose excretion in the urine (osmotic diuresis); dilutional hyponatremia can also occur due to the glucose-driven osmotic pull of water into the extracellular space.

(Choice B) High serum osmolality with low urine osmolality (dilute urine) can be seen in diabetes insipidus, a condition characterized by polyuria and excessive urinary water losses. However, diabetes insipidus is associated with a high or high/normal serum sodium, rather than this patient's hyponatremia. This patient also has no history of polyuria.

(Choice E) Low serum osmolality and low urine osmolality are characteristic of primary polydipsia, a disorder caused by excessive water intake. This disorder can be due to CNS disorders or psychotropic medications and is also associated with hyponatremia (ie, hypotonic hyponatremia). However, ADH levels are low, rather than increased, and patients often have polyuria. This patient has no history of excessive water intake or polyuria.

Educational objective:
Ectopic production of antidiuretic hormone (ADH) from malignancy can lead to the syndrome of inappropriate ADH secretion, a condition of impaired urinary water excretion. This condition manifests with low serum osmolality, hyponatremia, high urine osmolality, and high urine sodium.

References

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A 48-year-old woman comes to the office due to a 6-month history of involuntary passage of urine when sneezing or coughing. Recently, she has experienced urine leakage even with normal daily activity, which has been embarrassing and has caused her to limit social activities and quit playing tennis. The patient has no weakness, numbness, or fecal incontinence. She has hypertension and type 2 diabetes mellitus. The patient has had 4 uncomplicated vaginal deliveries. Supine blood pressure is 126/82 mm Hg and upright blood pressure is 120/80 mm Hg. Pelvic examination shows normal vaginal rugae and physiologic discharge. A small amount of urine leaks from the urethra when the patient is asked to cough. Neurologic examination is normal. Which of the following is the most likely cause of this patient's condition?

- A. Bladder outlet obstruction
- B. Detrusor muscle inactivity
- C. Detrusor muscle overactivity
- D. Diabetic autonomic neuropathy
- E. Urethral sphincter dysfunction

Submit

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- A. Bladder outlet obstruction (1%)
- ✗ B. Detrusor muscle inactivity (8%)
- C. Detrusor muscle overactivity (11%)
- D. Diabetic autonomic neuropathy (5%)
- ✓ E. Urethral sphincter dysfunction (72%)

Incorrect
Correct answer
E

72%
Answered correctly

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Explanation

Differential diagnosis of urinary incontinence		
	Etiology	Symptoms

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Differential diagnosis of urinary incontinence		
	Etiology	**Symptoms**
Stress	• ↓ Urethral sphincter tone • Urethral hypermobility	• Leakage with coughing, sneezing, lifting
Urge	• Detrusor overactivity	• Sudden, overwhelming urge to urinate
Overflow	• Impaired detrusor contractility • Bladder outlet obstruction	• Incomplete emptying & persistent involuntary dribbling

This patient has urinary incontinence. Continence is maintained by the bladder (detrusor muscle) and external and internal urinary sphincters. The **external urinary sphincter** (EUS) is a skeletal muscle that receives somatic motor innervation (voluntary control) from the perineal branches of the **pudendal nerve** (S2-S4). In contrast, the bladder and internal urethral sphincter (IUS) receive autonomic innervation: Sympathetic stimulation promotes urine storage and continence by increasing IUS tone and inhibiting detrusor contractions, and parasympathetic activity relaxes IUS tone and stimulates detrusor contractions, thereby promoting micturition.

Stress incontinence is the leakage of urine with increased intraabdominal pressure (eg, coughing). A common cause is urethral sphincter dysfunction, which usually occurs in women with multiple **prior vaginal deliveries**. Vaginal delivery is associated with obstetric trauma, which can cause urethral sphincter injury or pudendal nerve injury that contributes to decreased EUS tone. Because of **low urethral sphincter tone** and increasing pelvic floor laxity with age, sudden increases in intraabdominal pressure (eg, coughing, sneezing) can cause the pressure within the bladder to exceed the urethral closing pressure. This leads to **intermittent leakage** of urine.

(Choices A, B, and D) Bladder outlet obstruction (eg, tumor obstructing the urethra) and detrusor muscle inactivity (often secondary to diabetic autonomic neuropathy) both lead to urinary retention. In patients with urinary retention, urine slowly accumulates in the bladder until the intravesical pressure exceeds the urethral closing

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• Bladder outlet obstruction	

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Stress incontinence is the leakage of urine with increased intraabdominal pressure (eg, coughing). A common cause is urethral sphincter dysfunction, which usually occurs in women with multiple **prior vaginal deliveries**. Vaginal delivery is associated with obstetric trauma, which can cause urethral sphincter injury or pudendal nerve injury that contributes to decreased EUS tone. Because of **low urethral sphincter tone** and increasing pelvic floor laxity with age, sudden increases in intraabdominal pressure (eg, coughing, sneezing) can cause the pressure within the bladder to exceed the urethral closing pressure. This leads to **intermittent leakage** of urine.

(Choices A, B, and D) Bladder outlet obstruction (eg, tumor obstructing the urethra) and detrusor muscle inactivity (often secondary to diabetic autonomic neuropathy) both lead to urinary retention. In patients with urinary retention, urine slowly accumulates in the bladder until the intravesical pressure exceeds the urethral closing pressure, causing leakage. Because urine is constantly accumulating in the bladder, patients have persistent involuntary dribbling of urine (overflow incontinence) rather than urine leakage with cough. In addition, this patient's normal neurologic examination with no associated numbness or orthostatic hypotension makes diabetic autonomic neuropathy unlikely.

(Choice C) Detrusor overactivity is the underlying mechanism of urge incontinence, which typically presents with a sudden urge to urinate followed by the immediate, involuntary loss of urine. This patient's incontinence episodes typically follow an abrupt increase in intraabdominal pressure (eg, coughing, sneezing), making urge incontinence less likely.

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activity relaxes IUS tone and stimulates detrusor contractions, thereby promoting micturition.

Stress incontinence is the leakage of urine with increased intraabdominal pressure (eg, coughing). A common cause is urethral sphincter dysfunction, which usually occurs in women with multiple **prior vaginal deliveries**. Vaginal delivery is associated with obstetric trauma, which can cause urethral sphincter injury or pudendal nerve injury that contributes to decreased EUS tone. Because of **low urethral sphincter tone** and increasing pelvic floor laxity with age, sudden increases in intraabdominal pressure (eg, coughing, sneezing) can cause the pressure within the bladder to exceed the urethral closing pressure. This leads to **intermittent leakage** of urine.

(Choices A, B, and D) Bladder outlet obstruction (eg, tumor obstructing the urethra) and detrusor muscle inactivity (often secondary to diabetic autonomic neuropathy) both lead to urinary retention. In patients with urinary retention, urine slowly accumulates in the bladder until the intravesical pressure exceeds the urethral closing pressure, causing leakage. Because urine is constantly accumulating in the bladder, patients have persistent involuntary dribbling of urine (overflow incontinence) rather than urine leakage with cough. In addition, this patient's normal neurologic examination with no associated numbness or orthostatic hypotension makes diabetic autonomic neuropathy unlikely.

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Educational objective:
Stress incontinence, involuntary leakage of urine with increased intraabdominal pressure, can occur due to urethral sphincter dysfunction (eg, decreased sphincter tone). Risk factors include multiple prior vaginal deliveries, which can injure the external urethral sphincter or pudendal nerve.

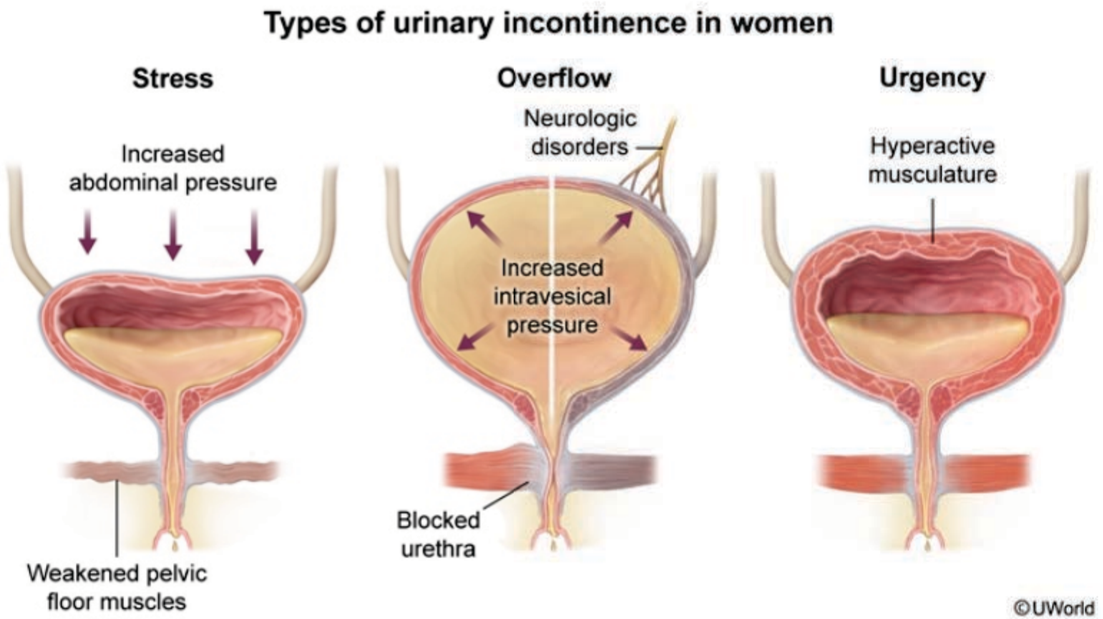
References

- Clinical and functional anatomy of the urethral sphincter.

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Urge	• Detrusor overactivity	• Sudden, overwhelming urge to urinate

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(Choice C) Detrusor overactivity is the underlying mechanism of urge incontinence, which typically presents with a sudden urge to urinate followed by the immediate, involuntary loss of urine. This patient's incontinence episodes

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A newborn boy is being evaluated in the delivery room due to respiratory distress. He was born at 37 weeks gestation to a 28-year-old primigravida via cesarean delivery due to breech presentation. The mother had limited prenatal care but was noted to have oligohydramnios during pregnancy. Examination of the infant is significant for a flattened nose and ears, recessed chin, and bilateral clubfoot deformity. Breath sounds are decreased bilaterally. This pattern of findings is best classified as which of the following?

- A. Association
- B. Dysplasia
- C. Mosaicism
- D. Polymorphism
- E. Sequence

Submit

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- A. Association (7%)
- ✗ B. Dysplasia (7%)
- C. Mosaicism (3%)
- D. Polymorphism (4%)
- ✓ E. Sequence (77%)

Incorrect
Correct answer
E

77%
Answered correctly

03 secs
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Explanation

Patterns of congenital anomalies		
Term	**Definition**	**Examples**
Association	• ≥2 anomalies that occur together more frequently than expected by chance alone • No known cause	• VACTERL association

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Patterns of congenital anomalies		
Term	**Definition**	**Examples**
Association	• ≥2 anomalies that occur together more frequently than expected by chance alone • No known cause	• VACTERL association
Syndrome	• Aggregate of anomalies that develop independently from each another • Caused by an underlying defect (eg, chromosomal abnormality, single gene defect, teratogen)	• Turner syndrome • Marfan syndrome • Fetal alcohol syndrome
Sequence	• Predictable series of anatomically related anomalies • Caused by an inciting event/primary anomaly that subsequently affects development of other structures	• Potter sequence • Pierre Robin sequence
VACTERL = **V**ertebral anomaly, **A**norectal malformation, **C**ardiovascular anomaly, **T**racheoesophageal fistula, **E**sophageal atresia, **R**enal &/or radial anomaly, **L**imb defect.		

A **sequence** is a predictable series of **anatomically related anomalies** that develop as a consequence of a known primary disturbance (ie, **cause-and-effect** relationship). In this case, the neonate has Potter sequence, a cascade of deformations due to severe **oligohydramnios**.

Low amniotic fluid is typically the result of a genitourinary tract anomaly (eg, bilateral renal agenesis) leading to impaired fetal urine production or preterm prelabor rupture of membranes. Regardless of the cause, insufficient

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VACTERL = **V**ertebral anomaly, **A**norectal malformation, **C**ardiovascular anomaly, **T**racheoesophageal fistula, **E**sophageal atresia, **R**enal &/or radial anomaly, **L**imb defect.

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Low amniotic fluid is typically the result of a genitourinary tract anomaly (eg, bilateral renal agenesis) leading to impaired fetal urine production or preterm prelabor rupture of membranes. Regardless of the cause, insufficient amniotic fluid causes **fetal constraint and compression**, and this abnormal mechanical force underlies the related anatomic defects of Potter sequence. Postnatal features include the following:

- **Pulmonary hypoplasia:** Restricted fetal thoracic expansion leads to alveolar collapse and impaired lung development. This is the most severe consequence of Potter sequence, manifesting as respiratory distress or decreased breath sounds; it is often fatal.
- **Flattened facies:** Extrinsic compression leads to the characteristic facial appearance of a flattened nasal bridge, low-set ears, and a recessed chin.
- **Skeletal anomalies:** Limited fetal movement leads to limb abnormalities such as contractures and clubfoot, as seen in this case.

Potter sequence has been inaccurately referred to as Potter syndrome. A syndrome is an aggregate of anomalies with a known underlying cause, usually genetic, such as Down syndrome. However, in a syndrome, the anomalies develop independently from one another rather than sequentially due to causal interaction.

(Choice A) An association is 2 or more anomalies that occur together more often than would be expected by chance alone but without a known cause. An example is VACTERL association (**V**ertebral anomaly, **A**norectal malformation, **C**ardiovascular anomaly, **T**racheoesophageal fistula, **E**sophageal atresia, **R**enal and/or radial anomaly, **L**imb defect).

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(Choice B) Dysplasia refers to the abnormal growth or development of a cell, tissue, or organ (eg, congenital hip dysplasia).

(Choice C) Mosaicism is the occurrence of 2 or more genetically distinct cells within the same patient (eg, mosaic Down syndrome).

(Choice D) Polymorphism refers to genetically distinct normal phenotypes within a population (eg, eye color).

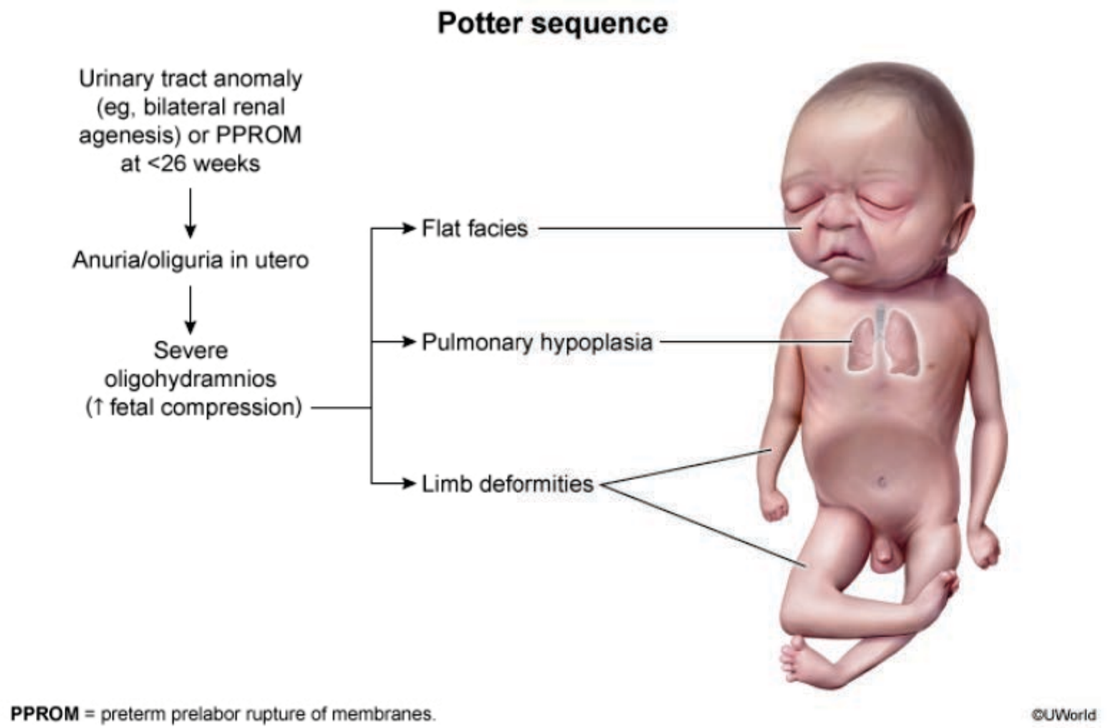
Educational objective:
A sequence is a predictable series of anatomically related anomalies that develop as a consequence of a known primary anomaly (ie, cause-and-effect relationship). Oligohydramnios leads to fetal compression and the predictable cascade of findings in Potter sequence (eg, pulmonary hypoplasia, facial and limb anomalies).

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chromosomal abnormality, single gene defect, teratogen)

- Fetal alcohol syndrome

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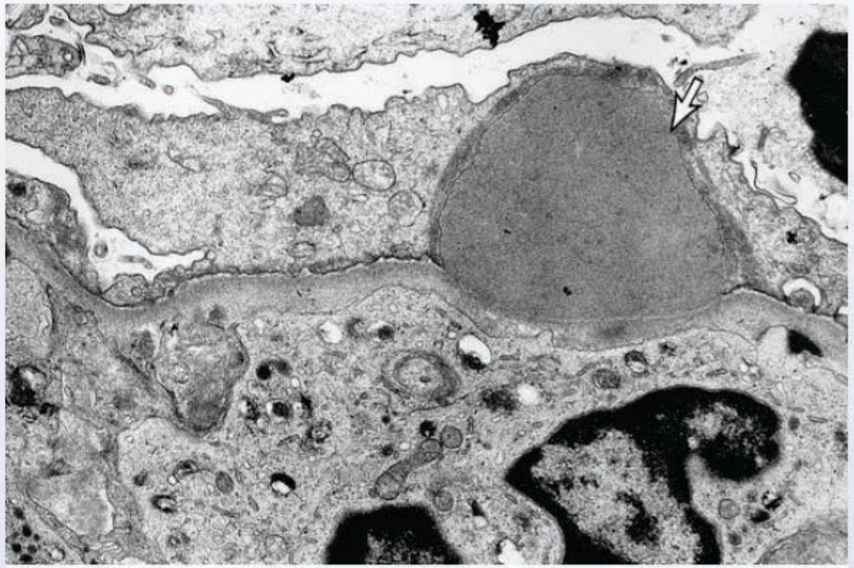
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as seen in this case.

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A 9-year-old girl is brought to the office due to 2 days of face and eye puffiness. The patient was treated for a rash on her leg with an antibiotic about 3 weeks ago. Temperature is 37.2 C (99 F) and blood pressure is 150/90 mm Hg. On physical examination, there is generalized edema but no rash. Urinalysis reveals proteinuria and hematuria. An electron microscopy image representative of this patient's disease process is shown below:



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The area marked by the arrow most likely represents which of the following?

- A. Albumin buildup
- B. Eosinophil enzymes
- C. Fibrin deposition
- D. Hyaline accumulation

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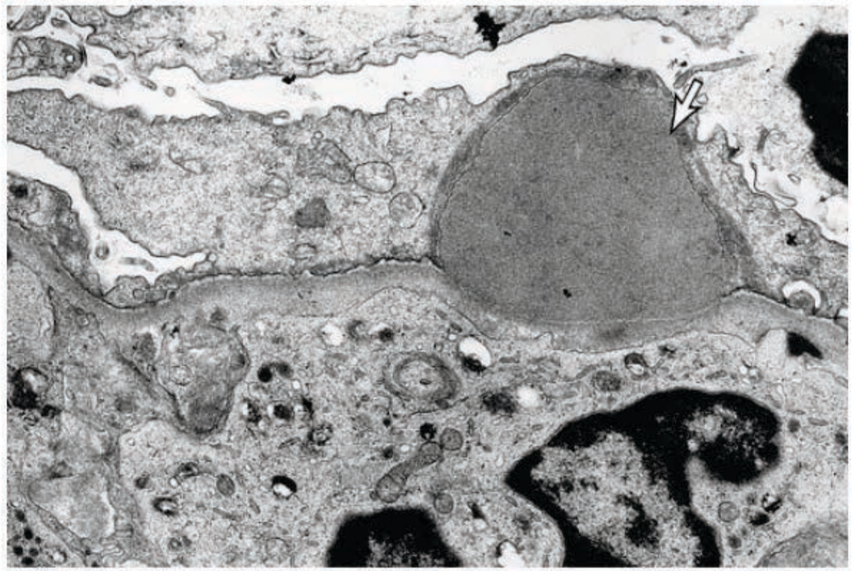
A 9-year-old girl is brought to the office due to 2 days of face and eye puffiness. The patient was treated for a rash on h
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D. Hyaline accumulation

E. Immune complex deposits

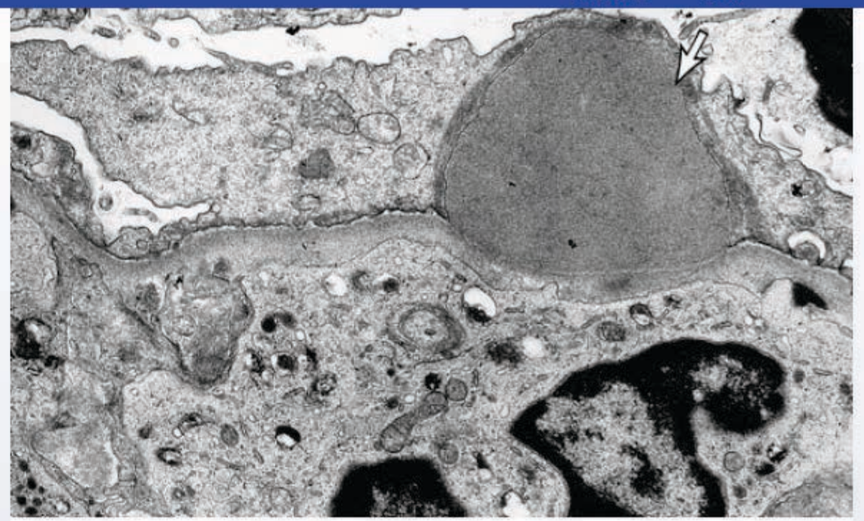
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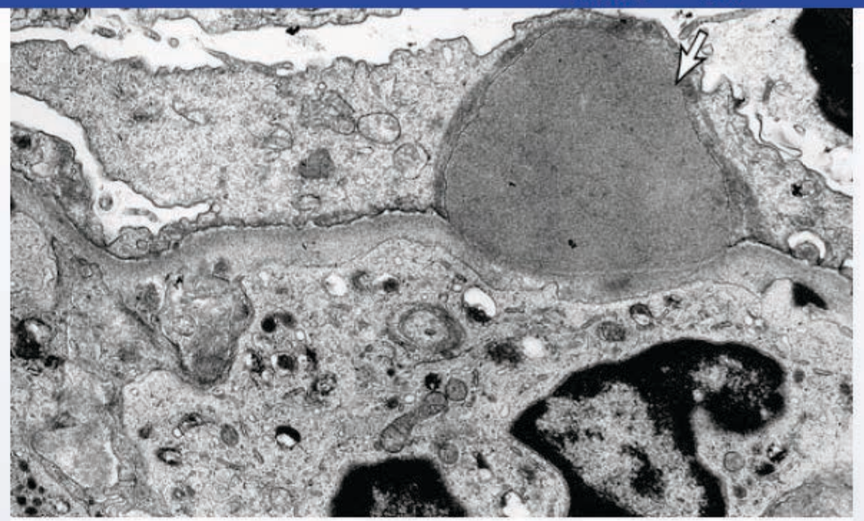
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The area marked by the arrow most likely represents which of the following?

- A. Albumin buildup
- B. Eosinophil enzymes
- C. Fibrin deposition
- D. Hyaline accumulation
- E. Immune complex deposits
- F. Lipid droplet
- G. Neutrophil enzymes

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The area marked by the arrow most likely represents which of the following?

- A. Albumin buildup (3%)
- B. Eosinophil enzymes (1%)
- C. Fibrin deposition (4%)
- D. Hyaline accumulation (4%)
- ✓ E. Immune complex deposits (81%)
- F. Lipid droplet (3%)
- G. Neutrophil enzymes (0%)

Correct

81% Answered correctly

15 secs Time Spent

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Explanation

Acute poststreptococcal glomerulonephritis	
Onset	• 7-10 days after GAS pharyngeal infection • 2-4 weeks after GAS skin infection
Pathophysiology	• Formation of nephritogenic GAS antigen-antibody complexes • Complex deposition along GBM • Complement activation & neutrophil-mediated damage (type III HS)
Clinical features*	• Gross hematuria (tea- or cola-colored urine) • Hypertension • Edema (periorbital or generalized)
Laboratory findings	• ↑ Serum creatinine with hematuria, RBC casts & mild proteinuria • ↑ Antistreptolysin-O & anti-DNase B titers
Histologic findings	• LM: hypercellular enlarged glomeruli • IF: granular IgG, IgM & C3 deposits with "lumpy-bumpy" appearance • EM: subepithelial "humps" (between podocytes & GBM)
* 50% of cases are asymptomatic. **EM** = electron microscopy; **GAS** = group A *Streptococcus*; **GBM** = glomerular	

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* 50% of cases are asymptomatic.

EM = electron microscopy; **GAS** = group A *Streptococcus*; **GBM** = glomerular basement membrane; **HS** = hypersensitivity; **IF** = immunofluorescence; **LM** = light microscopy.

This pediatric patient with hypertension, hematuria, proteinuria, and edema has a nephritic syndrome. The timeline

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This pediatric patient with hypertension, hematuria, proteinuria, and edema has a nephritic syndrome. The timeline (3 weeks after a skin infection) of symptoms suggests the most likely cause is **poststreptococcal glomerulonephritis** (PSGN), an immune complex–mediated disease that occurs after exposure to nephritogenic strains of group A *Streptococcus*. Laboratory evaluation reveals classic signs of nephritic syndrome (eg, hematuria, red blood cell [RBC] casts, mild proteinuria).

The **immune complexes** in PSGN are deposited along the glomerular basement membrane (GBM) and are visible on electron microscopy as large, dome-shaped, **subepithelial**, electron-dense **deposits** ("humps"). These can also be visualized on immunofluorescence as **granular** deposits of IgG, IgM, and C3 along the GBM and glomerular mesangium ("**lumpy-bumpy**" appearance). Because the immune complexes trigger an inflammatory reaction, light microscopy shows large glomeruli that are hypercellular due to leukocyte infiltration and proliferation of glomerular cells (a response to injury).

(Choice A) Proteins such as albumin may be lost in the urine due to increased permeability of the glomerular capillary wall in PSGN. However, albumin does not deposit within the glomerulus or renal tubules.

(Choice B) Many antibiotics (eg, penicillins, cephalosporins) can cause acute interstitial nephritis (AIN), which often manifests as peritubular T-lymphocyte, macrophage, and eosinophilic infiltration. However, edema, significant hematuria, and proteinuria are uncommon, and AIN usually resolves when the offending agent is discontinued.

(Choice C) Prominent fibrin deposition is characteristic of rapidly progressive (crescentic) glomerulonephritis.

(Choice D) Hyaline (acellular, homogeneous, proteinaceous material) can accumulate within the glomerular capillary and arteriolar walls in diabetic nephropathy due to extravasation of plasma proteins.

(Choice F) Lipid droplets in renal tubules may be seen in conditions causing nephrotic syndrome, which leads to heavy proteinuria and edema; however, gross hematuria and RBC casts are unexpected. In addition, lipid droplets do not deposit on the basement membrane.

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(Choice F) Lipid droplets in renal tubules may be seen in conditions causing nephrotic syndrome, which leads to heavy proteinuria and edema; however, gross hematuria and RBC casts are unexpected. In addition, lipid droplets do not deposit on the basement membrane.

(Choice G) Neutrophils and monocytes infiltrate the glomeruli in PSGN, contributing to the hypercellular appearance on light microscopy. Enzymes released from these cells would not typically form extracellular aggregates.

Educational objective:
Poststreptococcal glomerulonephritis is an immune complex–mediated disease that occurs 2-4 weeks after group A *Streptococcus* skin infections. Immune complexes composed of IgG, IgM, and C3 are deposited along the glomerular basement membrane and are visible on electron microscopy as large, dome-shaped, subepithelial, electron-dense deposits.

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- LM: hypercellular enlarged glomeruli

Exhibit Display

Nephritic vs nephrotic syndrome

	Nephritic	Nephrotic
Proteinuria	Mild	Significant (>3.5 g/day)
Serum albumin	Normal	Decreased
Edema	Mild	Significant
GFR	Decreased	Normal
Hypertension	Yes	No
Hematuria	Yes	No
Pyuria	Yes	No
Casts	RBC	Fatty or none

GFR = glomerular filtration rate; **RBC** = red blood cell.

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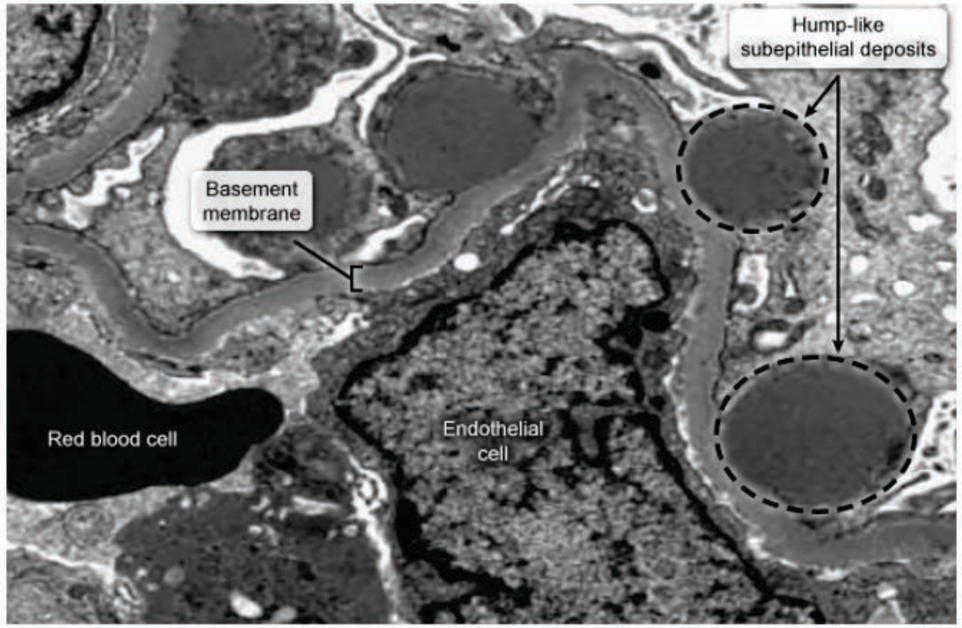
often manifests as peritubular T-lymphocyte, macrophage, and eosinophilic infiltration. However, edema,

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- LM: hypercellular enlarged glomeruli

Exhibit Display

Poststreptococcal glomerulonephritis



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A 55-year-old man comes to the hospital due to progressive fatigue and weakness. Medical history includes type 2 diabetes mellitus and obesity. Laboratory results are as follows:

Serum chemistry

Sodium	138 mEq/L
Chloride	110 mEq/L
Bicarbonate	18 mEq/L

Which of the following is the most likely diagnosis?

- A. Diabetic ketoacidosis
- B. Lactic acidosis
- C. Obesity hypoventilation
- D. Primary hyperaldosteronism
- E. Renal tubular acidosis

Submit

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Serum chemistry

Sodium	138 mEq/L
Chloride	110 mEq/L
Bicarbonate	18 mEq/L

Which of the following is the most likely diagnosis?

- A. Diabetic ketoacidosis (7%)
- ✗ B. Lactic acidosis (12%)
- C. Obesity hypoventilation (17%)
- D. Primary hyperaldosteronism (2%)
- ✓ E. Renal tubular acidosis (59%)

Incorrect
Correct answer
E

59%
Answered correctly

11 mins, 10 secs
Time Spent

2023
Version

Explanation

Metabolic acidosis		
Type	Normal anion gap	Elevated anion gap

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Explanation

Metabolic acidosis		
Type	**Normal anion gap**	**Elevated anion gap**
Mechanism	• Loss of bicarbonate	• Accumulation of unmeasured acidic compounds
Common causes	• Severe diarrhea • Renal tubular acidosis • Excessive saline infusion	• Lactic acidosis • Diabetic ketoacidosis • Renal failure (uremia) • Methanol, ethylene glycol • Salicylate toxicity

This patient has low serum bicarbonate (HCO_3^-) (<24 mEq/L), consistent with metabolic acidosis. The anion gap is normal at 10 mEq/L; therefore, the most likely diagnosis is **renal tubular acidosis**, a common cause of **nonanion gap metabolic acidosis** (NAGMA).

NAGMA results from **loss of HCO_3^-** (usually from the kidneys or gastrointestinal tract), leading to a relative increase in H^+. In renal tubular acidosis, there is either impaired proximal tubular HCO_3^- reabsorption (type 2) or impaired distal tubular H^+ secretion (types 1 and 4) leading to net HCO_3^- loss. Severe diarrhea, involving loss of HCO_3^- in the stool, is another common cause of NAGMA.

NAGMA is also referred to as **hyperchloremic acidosis** because the decrease in serum HCO_3^- is compensated for by an increase in serum Cl^- to maintain electronegative balance.

(Choices A and B) Anion gap metabolic acidosis results from the addition of unmeasured acidic compounds to the blood. The compounds donate H^+ to bind up serum HCO_3^-, reducing buffering capacity and causing metabolic

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(Choices A and B) Anion gap metabolic acidosis results from the addition of unmeasured acidic compounds to the blood. The compounds donate H^+ to bind up serum HCO_3^-, reducing buffering capacity and causing metabolic acidosis. The remaining anionic component increases the anion gap. Common etiologies of anion gap metabolic acidosis include increased production of ketones (eg, acetoacetate, beta-hydroxybutyrate), which occurs with diabetic ketoacidosis, and increased production of lactic acid, which occurs with reduced organ and tissue perfusion (eg, sepsis).

(Choice C) Hypoventilation causes retention of CO_2 and respiratory acidosis. A compensatory metabolic alkalosis with increased serum HCO_3^- (>24 mEq/L) is expected.

(Choice D) Primary hyperaldosteronism causes excessive loss of H^+ from the renal tubular collecting duct, leading to metabolic alkalosis with increased serum HCO_3^-.

Educational objective:
Nonanion gap metabolic acidosis (NAGMA) results from the loss of bicarbonate (HCO_3^-) (usually from the kidneys or gastrointestinal tract), leading to a relative increase in H^+. Common causes include renal tubular acidosis and severe diarrhea. NAGMA is also referred to as hyperchloremic acidosis because the decrease in serum HCO_3^- is

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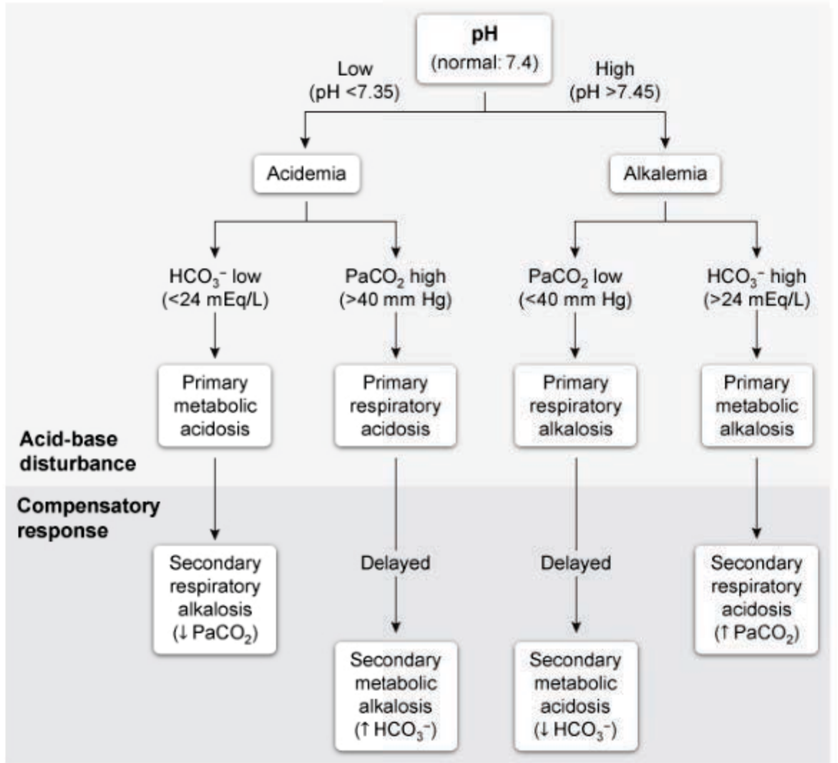
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Metabolic acidosis

Exhibit Display

Arterial blood gas interpretation of acid-base disorders



* The normal ranges for $PaCO_2$ and HCO_3^- vary slightly around 40 mm Hg and 24 mEq/L.
For simplicity, these numbers should be used as a normal baseline for acid-base calculations.

HCO_3^- = bicarbonate; **$PaCO_2$** = partial pressure of carbon dioxide in arterial blood.

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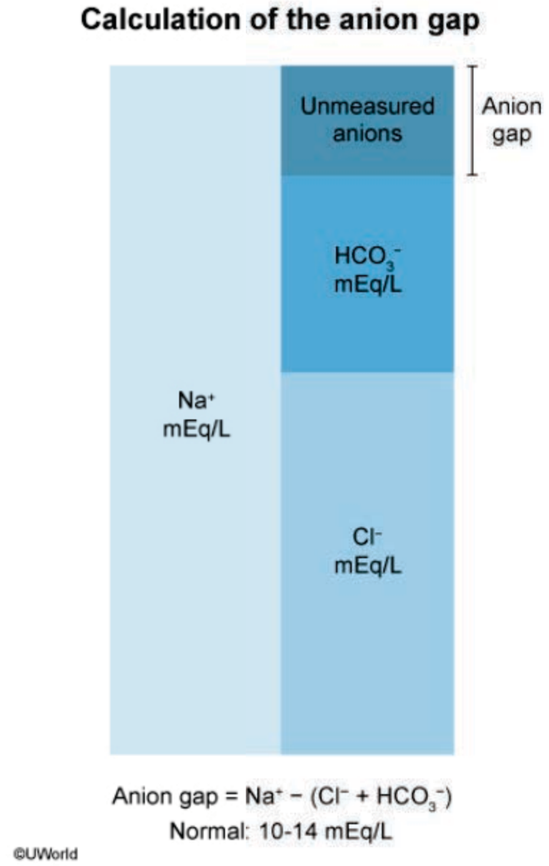
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acidosis include increased production of ketones (eg, acetoacetate, beta-hydroxybutyrate), which occurs with diabetic ketoacidosis, and increased production of lactic acid, which occurs with reduced organ and tissue

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Metabolic acidosis

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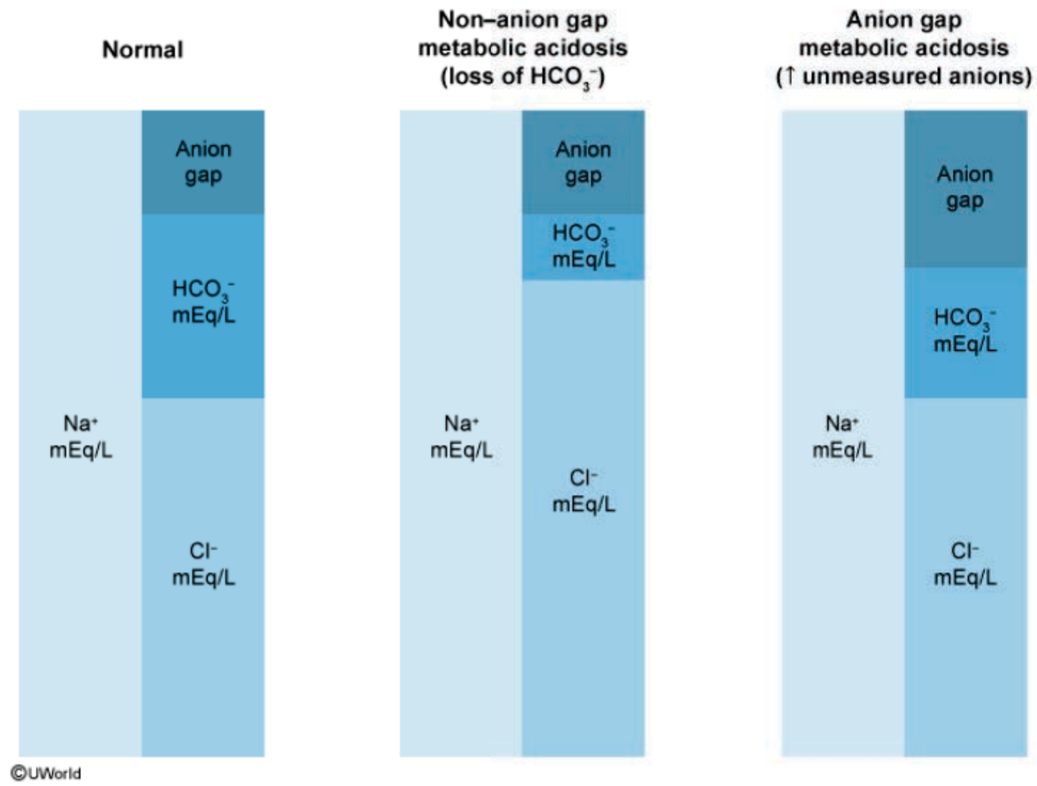
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Common	• Severe diarrhea	• Diabetic ketoacidosis

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A 62-year-old hospitalized man is evaluated due to acute renal failure. The patient was hospitalized 3 days ago due to precordial chest pain. During admission, he was found to have an elevated troponin I level but no ST-segment elevation on ECG; subsequent percutaneous catheterization with injection of contrast dye revealed 3-vessel coronary artery disease. The patient has continued to receive medical treatment while awaiting coronary artery bypass graft surgery. Today, he has elevated blood urea nitrogen and serum creatinine levels. The patient has had no fever, and blood pressure and heart rate have been within normal limits. Physical examination shows no new findings. Which of the following changes are most likely to be present in this patient's kidneys?

- A. Diffuse necrosis of the proximal tubular cells
- B. Extensive crescents in the glomeruli
- C. Fibrin-like material lining the arteriolar walls
- D. Mononuclear cell infiltrate in the interstitium
- E. Neutrophil aggregates in the interstitium and tubules

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- ✓ A. Diffuse necrosis of the proximal tubular cells (64%)
- ✗ B. Extensive crescents in the glomeruli (6%)
- C. Fibrin-like material lining the arteriolar walls (15%)
- D. Mononuclear cell infiltrate in the interstitium (6%)
- E. Neutrophil aggregates in the interstitium and tubules (8%)

Incorrect
Correct answer
A

64%
Answered correctly

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Explanation

Contrast-induced nephropathy	
Presentation	• Acute rise in serum creatinine and blood urea nitrogen 24-48 hr after contrast administration, followed by a gradual return to baseline

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Contrast-induced nephropathy	
Presentation	• Acute rise in serum creatinine and blood urea nitrogen 24-48 hr after contrast administration, followed by a gradual return to baseline
Etiology	• Direct cytotoxicity of intravenous contrast on tubular cells • Renal vasoconstriction
Laboratory findings	• Histology: extensive necrosis of proximal tubular cells • Muddy brown casts on urinalysis

This patient developed acute kidney injury after undergoing percutaneous catheterization, a procedure that uses contrast material to evaluate the patency of the coronary arteries. In a patient with normal vital signs (ie, no history of recent hypotension to suggest renal tubular ischemia), this presentation suggests **contrast-induced nephropathy** (CIN). Patients with CIN typically have an acute rise in creatinine and blood urea nitrogen within 24-48 hours of contrast administration, followed by a gradual return to baseline.

The etiology of CIN remains unclear but is likely multifactorial and includes the following:

- Direct cytotoxicity causing **diffuse necrosis of the proximal tubular cells** visible on histologic specimens and **muddy brown casts** on urinalysis (acute tubular necrosis)
- Renal vasoconstriction causing medullary ischemia

Preventive measures include avoidance of nonsteroidal anti-inflammatory drugs, which can worsen vasoconstriction, periprocedural administration of intravenous normal saline, and use of the smallest possible volume of contrast medium.

(Choice B) Glomerular crescents are seen in crescentic glomerulonephritis, which can occur in multiple renal diseases (eg, Goodpasture syndrome, microscopic polyangiitis). However, patients typically have nephritic syndrome, which is characterized by hematuria with red blood cell casts, hypertension, and edema.

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(Choice C) Fibrinoid necrosis is visualized histologically as fibrin material lining the arteriolar walls. This pattern is typically seen in the setting of hypertensive (malignant) nephrosclerosis, in which a markedly elevated blood pressure causes vascular endothelial damage. This patient's blood pressure has been normal.

(Choice D) Mononuclear cell infiltrate in the interstitium is consistent with interstitial nephritis. Interstitial nephritis typically occurs after the initiation of new drugs (eg, penicillin, cephalosporin), typically with fever, rash, and sterile pyuria.

(Choice E) Neutrophil aggregates in the interstitium and tubular lumina are a feature of acute pyelonephritis, which is caused by an ascending bacterial infection through the urinary tract. It typically presents with fever, nausea, vomiting, flank pain, and costovertebral tenderness.

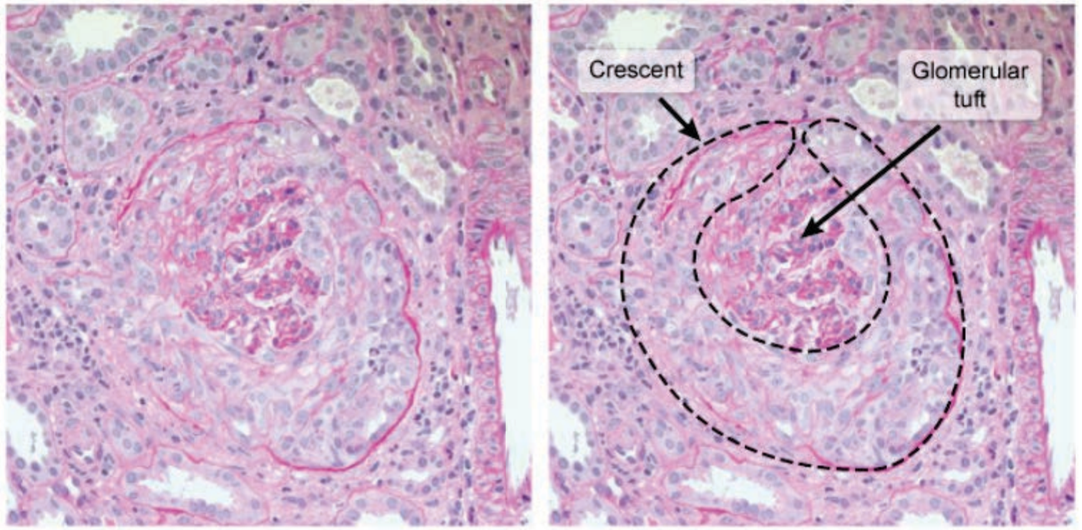
Educational objective:
Contrast-induced nephropathy is characterized by an acute rise in creatinine and blood urea nitrogen after radiologic contrast administration, followed by a gradual return to baseline. It is characterized histologically by diffuse necrosis of the proximal tubular cells (acute tubular necrosis). Urinalysis usually demonstrates muddy brown casts.

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- Direct cytotoxicity causing **diffuse necrosis of the proximal tubular cells** visible on histologic specimens

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Crescentic glomerulonephritis



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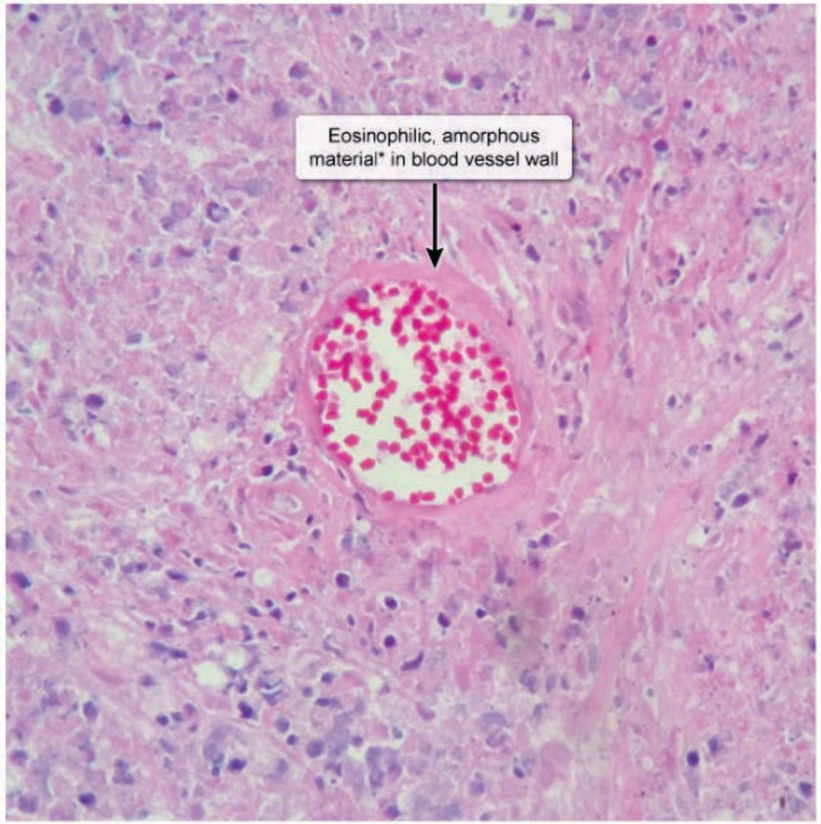
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- Direct cytotoxicity causing **diffuse necrosis of the proximal tubular cells** visible on histologic specimens

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Fibrinoid necrosis



*Fibrin deposition.

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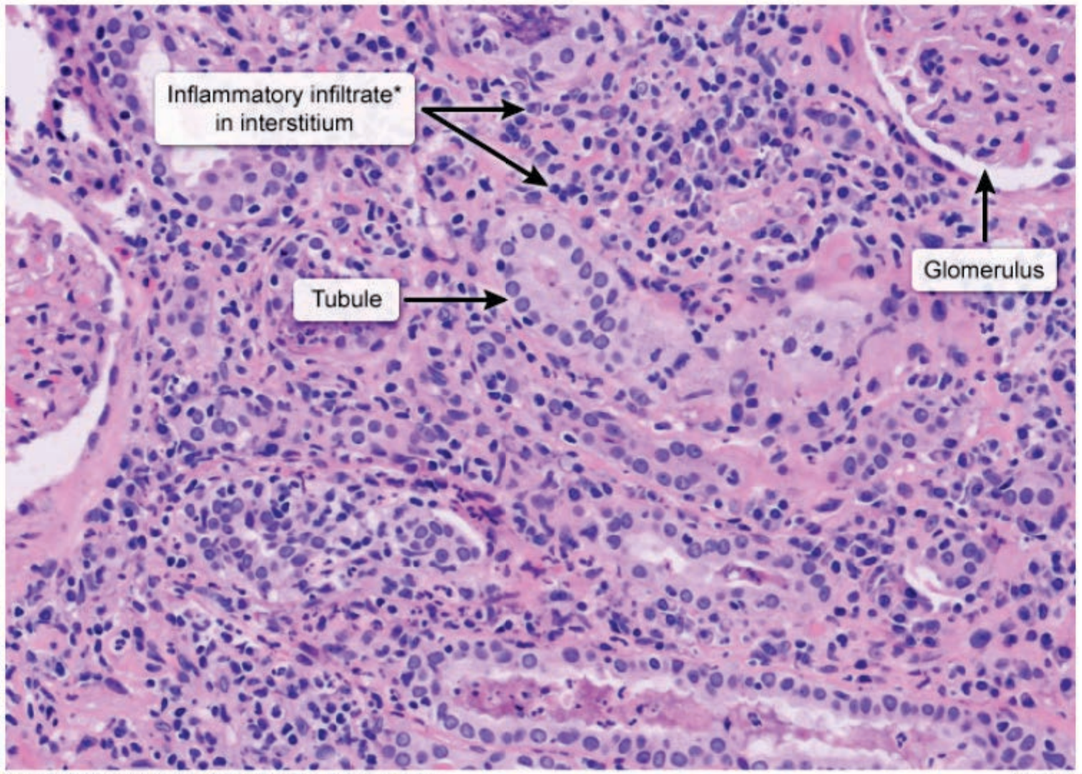
brown casts.

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- Direct cytotoxicity causing **diffuse necrosis of the proximal tubular cells** visible on histologic specimens

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Interstitial nephritis



*Predominantly mononuclear cells (eg, lymphocytes).

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brown casts.

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A 60-year-old woman is being evaluated for abnormal renal function. She is found to have a serum creatinine of 2.2 mg/dL on routine laboratory monitoring; her creatinine level a year ago was 1.2 mg/dL. The patient has a history of nonischemic cardiomyopathy and systolic heart failure and has been on a stable medical regimen for the past 2 years. She has no dyspnea, fever, rash, or lower extremity swelling but has been taking ibuprofen for 2 weeks due to left knee osteoarthritis. Urinalysis reveals the following:

Protein	none
White blood cells	none
Red blood cells	none
Sediment	none

Ibuprofen is discontinued, and her kidney function returns to normal in a week. Which of the following best explains this patient's transient deterioration in renal function?

- A. Impaired afferent arteriolar vasodilation
- B. Impaired efferent arteriolar vasodilation
- C. Interstitial inflammation
- D. Toxic injury to the proximal tubules
- E. Vasculitis of the glomerular capillaries

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Red blood cells	none
Sediment	none

Ibuprofen is discontinued, and her kidney function returns to normal in a week. Which of the following best explains this patient's transient deterioration in renal function?

- ✓ A. Impaired afferent arteriolar vasodilation (77%)
- ✗ B. Impaired efferent arteriolar vasodilation (6%)
- C. Interstitial inflammation (10%)
- D. Toxic injury to the proximal tubules (5%)
- E. Vasculitis of the glomerular capillaries (0%)

Incorrect
Correct answer
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77%
Answered correctly

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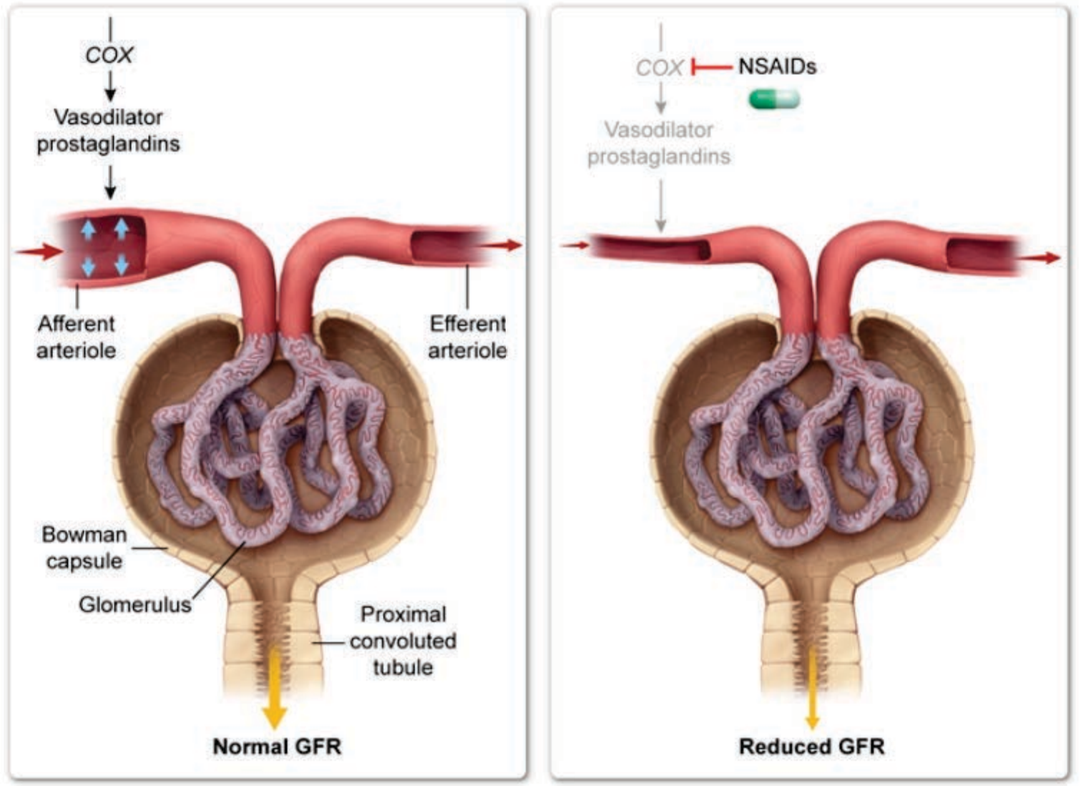
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the inhibition of the cyclooxygenase enzymes. These enzymes are the rate-limiting step in the formation of

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COX = cyclooxygenase; GFR = glomerular filtration rate

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This patient developed acute kidney injury after taking ibuprofen. **Nonsteroidal anti-inflammatory drugs** (NSAIDs) (eg, ibuprofen, aspirin, naproxen) exert their anti-inflammatory, analgesic, and antipyretic effects through the inhibition of the cyclooxygenase enzymes. These enzymes are the rate-limiting step in the formation of prostanoids (ie, prostaglandins, thromboxane), which are involved in mediating pain and inflammation.

Prostaglandins also help maintain renal perfusion by dilating the afferent arteriole, particularly in patients with intravascular volume depletion (eg, congestive heart failure, diarrhea, excessive diuresis) or chronic kidney disease. In such patients, **increased prostaglandin synthesis** is necessary to **preserve renal blood flow** and maintain glomerular filtration rate. In at-risk patients, **inhibition of afferent dilation** with NSAIDs results in reduced glomerular filtration and **prerenal azotemia** with elevations in creatinine and blood urea nitrogen (ratio >20:1).

NSAID-induced acute kidney injury is often diagnosed incidentally on laboratory tests performed for other reasons, and patients are generally asymptomatic. **Urinalysis** is typically **bland** without proteinuria, hematuria, or casts. Prolonged NSAID use can cause chronic kidney disease (analgesic nephropathy) due to papillary necrosis and chronic interstitial nephritis.

(Choice B) Activation of the renin-angiotensin-aldosterone system results in efferent arteriole constriction, and ACE inhibitors (eg, lisinopril) cause efferent vasodilation. These medications can cause acute kidney injury, particularly in patients with volume depletion or bilateral renal artery stenosis. However, NSAID-induced kidney injury is due to impaired afferent arteriole vasodilation.

(Choice C) NSAIDs are a common cause of acute interstitial nephritis (AIN). However, urinalysis in AIN typically demonstrates white blood cells and white blood cell casts, and patients commonly develop fevers and rash.

(Choice D) Acute tubular necrosis (ATN) can occur due to toxic (eg, aminoglycosides, radiocontrast agents) or ischemic (eg, hypotension) insults. However, urinalysis would demonstrate muddy-brown, granular casts, and NSAIDs are not commonly associated with ATN.

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(Choice E) Vasculitis involving the glomerular capillaries (eg, granulomatosis with polyangiitis, microscopic polyangiitis) causes a nephritic syndrome; urinalysis would demonstrate red blood cells and red blood cell casts. In addition, patients with vasculitides typically have associated systemic symptoms (eg, fever, fatigue, weight loss).

Educational objective:
Patients with intravascular volume depletion (eg, congestive heart failure, diarrhea, excessive diuresis) and chronic kidney disease depend on renal prostaglandin production to dilate the afferent glomerular arteriole and maintain the glomerular filtration rate. Nonsteroidal anti-inflammatory drugs inhibit prostaglandin synthesis, which can cause prerenal azotemia in at-risk patients.

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A 65-year-old man comes to the emergency department due to severe lower abdominal pain and nausea. He also has not been able to urinate for the past 24 hours. The patient has a history of hypertension and benign prostatic hyperplasia. On examination, a large mass is palpable in the suprapubic area. Multiple attempts at urethral catheterization are unsuccessful, and an ultrasound-guided midline suprapubic cystostomy is planned. Besides the bladder wall, which of the following structures is most likely to be penetrated by the trocar and cannula during the procedure?

- A. Anterior abdominal aponeurosis
- B. Parietal peritoneum
- C. Perineal membrane
- D. Ureter
- E. Visceral peritoneum

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- ✓ A. Anterior abdominal aponeurosis (53%)
- ✗ B. Parietal peritoneum (17%)
- C. Perineal membrane (8%)
- D. Ureter (5%)
- E. Visceral peritoneum (15%)

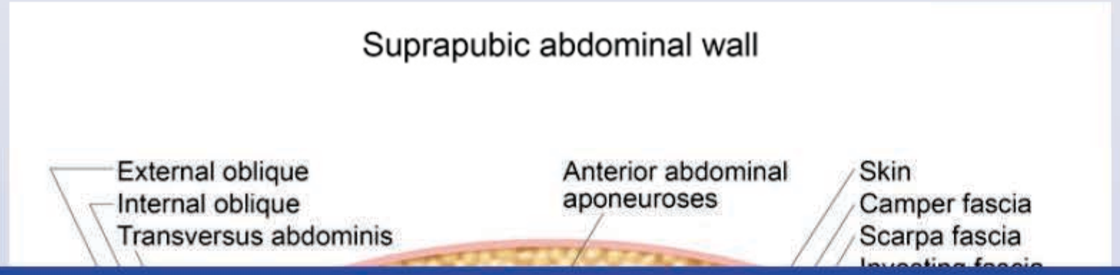
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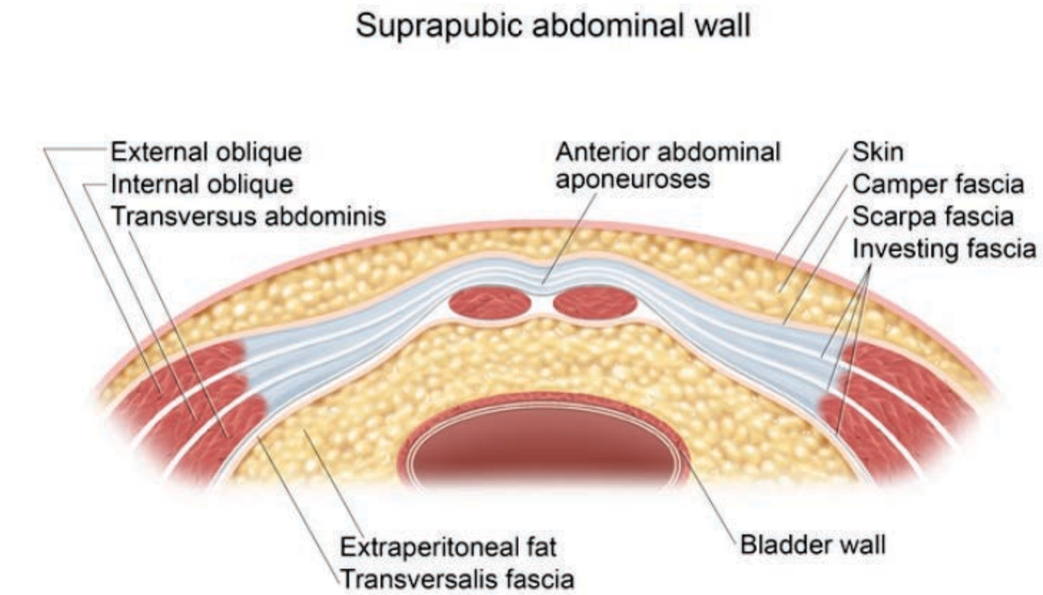
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E. Visceral peritoneum (15%)

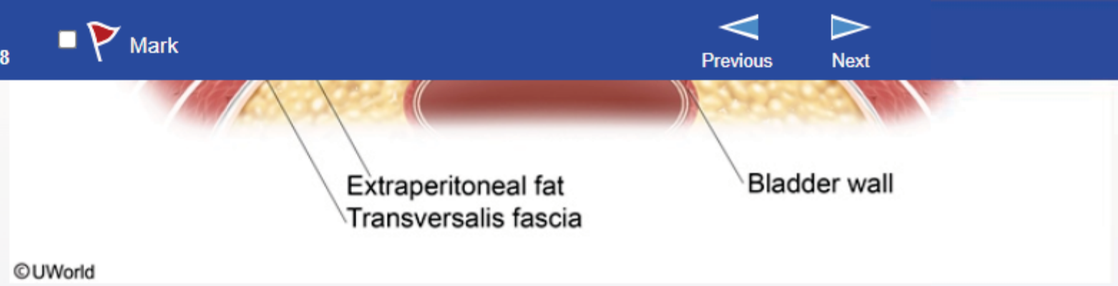
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lateral margins of the bladder, the peritoneum is reflected onto the lateral pelvic walls. The **bladder** is therefore

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This patient has a severe bladder outlet obstruction, with the bladder palpable above the pelvic brim. The superior surface of the bladder is covered with peritoneum and is found below coils of ileum or sigmoid colon. Along the lateral margins of the bladder, the peritoneum is reflected onto the lateral pelvic walls. The **bladder** is therefore **extraperitoneal**. As the bladder fills and bulges upward, it comes into direct contact with the anterior abdominal wall anteroinferior to the peritoneal space.

In a **suprapubic cystostomy**, the trocar and cannula pierces the **aponeurosis** of the abdominal wall muscles, along with the layers of the superficial fascia, transversalis fascia, and extraperitoneal fat. However, the peritoneum is not entered **(Choices B and E)**, reducing the risk of peritonitis and hemoperitoneum.

(Choice C) The perineal membrane (inferior fascia of the urogenital diaphragm) spans the deep perineal pouch from the periosteum of the ischiopubic rami to the arcuate ligament of the pubis. It is penetrated by the urethra inferior to the bladder but would not be encountered in suprapubic cystostomy.

(Choice D) The ureters enter the bladder posterolaterally at the lateral angle of the bladder. A suprapubic trocar enters anteriorly and will not encounter the ureters unless it passes through the body of the bladder.

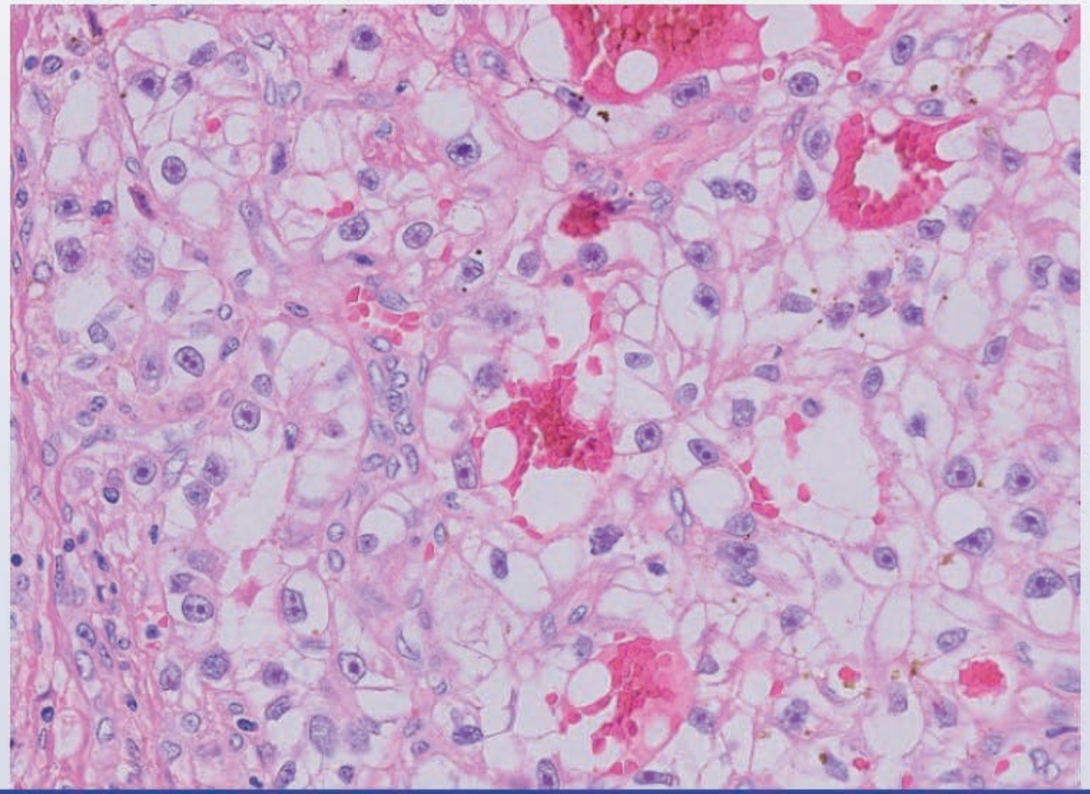
Educational objective:
The bladder is extraperitoneal. In placement of a suprapubic cystostomy, the trocar and cannula will pierce the layers of the abdominal wall but will not enter the peritoneum.

Anatomy	Renal, Urinary Systems & Electrolytes	Urinary retention
Subject	System	Topic

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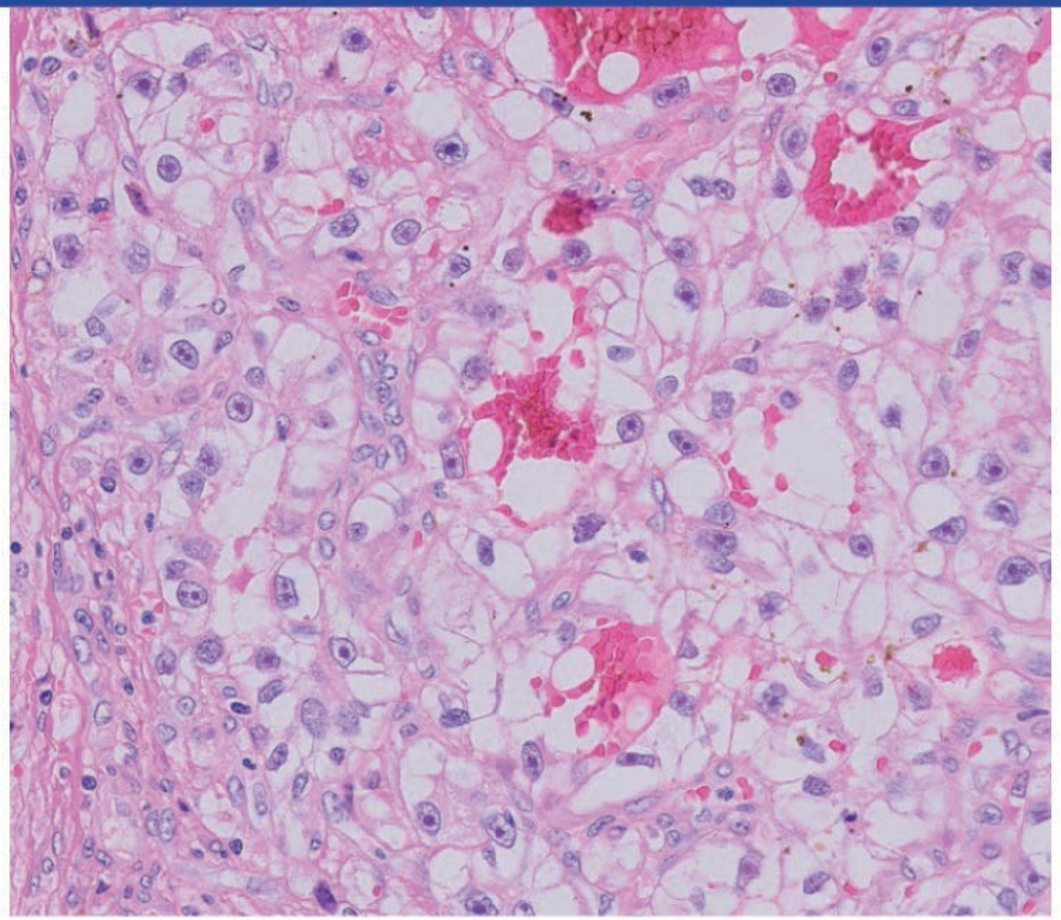
A 68-year-old woman comes to the office due to increasing low back pain. The pain is constant and worsens at night. She has also had a 6.8-kg (15-lb) weight loss over the past 3 months. Medical history is significant for osteoporosis and hypothyroidism. Family history is significant for breast cancer in her mother. She has smoked 1 pack of cigarettes daily for 30 years and drinks 1 or 2 glasses of wine every day. The patient immigrated to the United States from China 30 years ago; she mainly eats food she cooks herself. Vital signs are within normal limits. Physical examination shows point tenderness over the L3 and L4 vertebrae. MRI reveals lytic bone lesions in the corresponding vertebrae and also a right lower pole kidney mass. Histologic examination of the mass is shown below:



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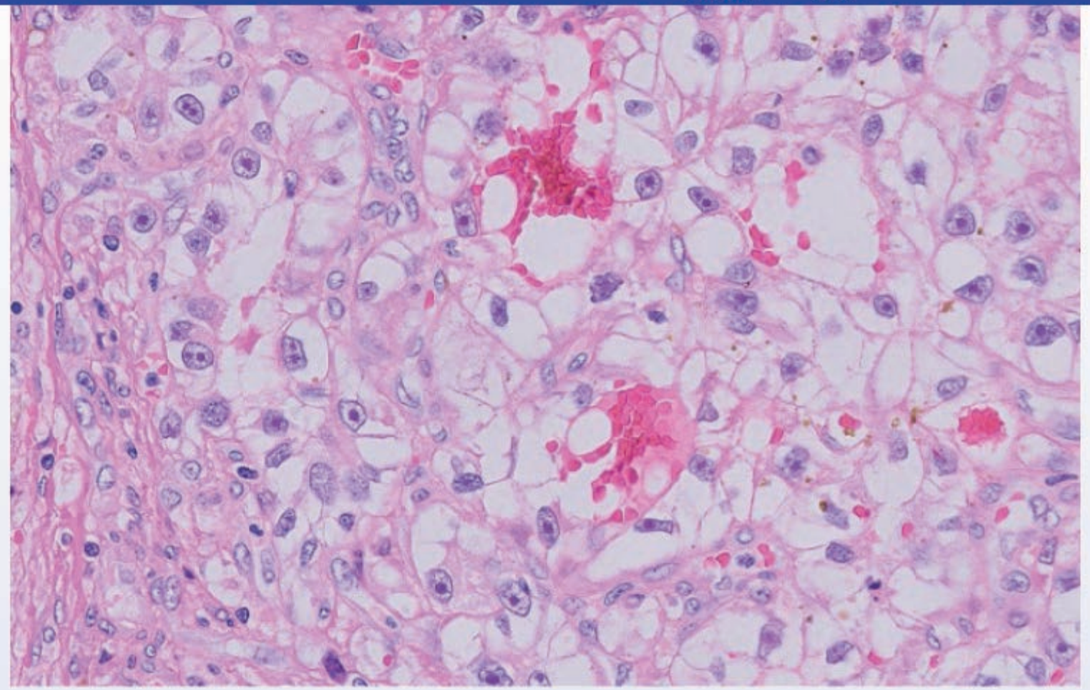
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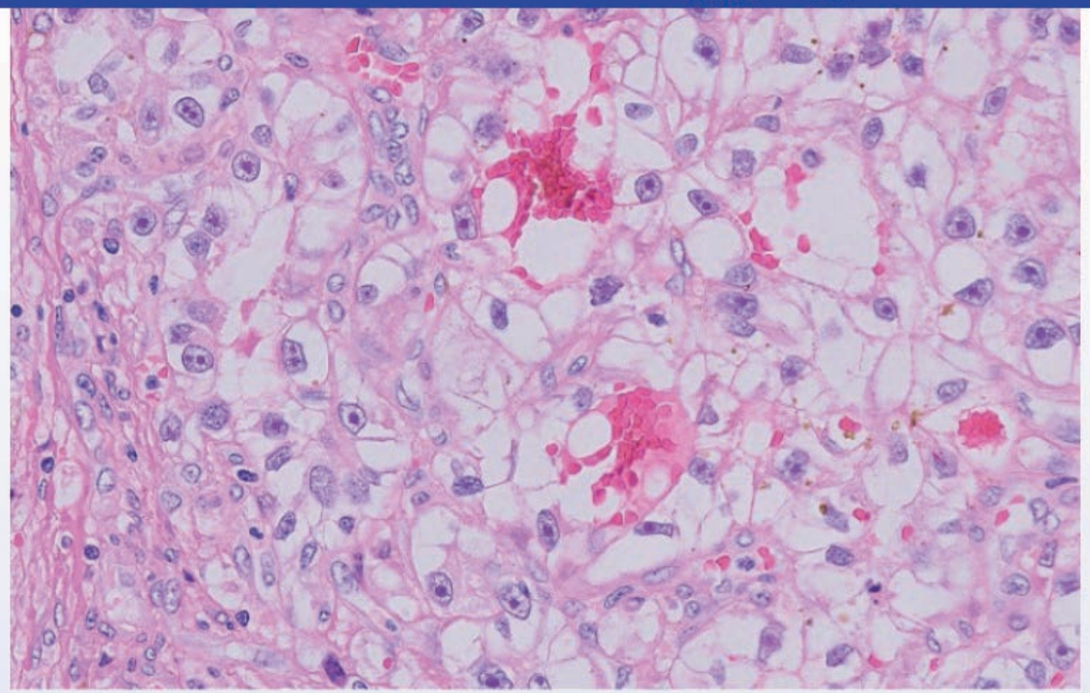


Which of the following risk factors most likely contributed to this patient's current condition?

- A. Alcohol use
- B. Diet
- C. Ethnicity
- D. Family history
- E. Smoking

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Which of the following risk factors most likely contributed to this patient's current condition?

- A. Alcohol use (0%)
- ✕ B. Diet (2%)
- C. Ethnicity (4%)
- D. Family history (8%)
- ✓ E. Smoking (84%)

Incorrect
Correct answer
E

84%
Answered correctly

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Renal cell carcinoma	
Presentation	• Hematuria, flank pain, palpable abdominal mass • Paraneoplastic syndrome (eg, polycythemia, hypercalcemia)
Risk factors	• Smoking, hypertension, obesity • Toxin exposure (eg, heavy metal, petroleum by-products)
Gross examination	• Spherical mass, often with invasion of the renal vein • Golden-yellow tissue (due to high lipid content)
Histology (Clear cell)	• Cuboidal or polygonal cells with abundant, clear cytoplasm • Branching, "chicken-wire" vasculature

This patient with back pain, osteolytic bone lesions, and histologic findings demonstrating rounded, **polygonal clear cells** has metastatic **renal cell carcinoma** (RCC). RCC is often asymptomatic until the disease is advanced, and many patients have metastatic disease at the time of diagnosis. Symptoms often include some combination of hematuria, abdominal mass, or flank pain; however, this classic triad occurs in <10% of cases. Systemic symptoms (eg, fever, weight loss, fatigue) and symptoms related to metastases (eg, bone pain) are common.

Risk factors for RCC include **smoking**, toxin exposure (eg, trichloroethylene, asbestos, petroleum by-products), obesity, and hypertension.

(Choice A) Alcohol use increases the risk of hepatocellular carcinoma and squamous cell carcinoma of the esophagus but is associated with a decreased risk of RCC.

(Choice B) Diets high in cured meat and salt-preserved foods (which are prevalent in some Asian populations) are associated with an increased risk of gastric cancer but not RCC.

(Choice C) Asian-American patients have a lower risk of RCC than other ethnicities. Individuals of Asian heritage

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(Choice C) Asian-American patients have a lower risk of RCC than other ethnicities. Individuals of Asian heritage are at increased risk of developing IgA nephropathy.

(Choice D) Patients with a strong family history of RCC (eg, first degree relative diagnosed before age 40) or those with certain hereditary cancer syndromes (eg, Von Hippel-Lindau disease) are at increased risk of RCC. In contrast, a strong family history of breast cancer may be associated with *BRCA* gene positivity and places patients at higher risk for breast and ovarian cancers.

Educational objective:
Renal cell carcinoma may present with a combination of hematuria, abdominal mass, or flank pain; however, this triad occurs together in <10% of cases. Pathology demonstrates rounded, polygonal cells with clear cytoplasm. Risk factors include smoking, toxin exposure, and certain hereditary disorders (eg, von Hippel-Lindau syndrome).

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This patient with back pain, osteolytic bone lesions, and histologic findings demonstrating rounded, **polygonal**

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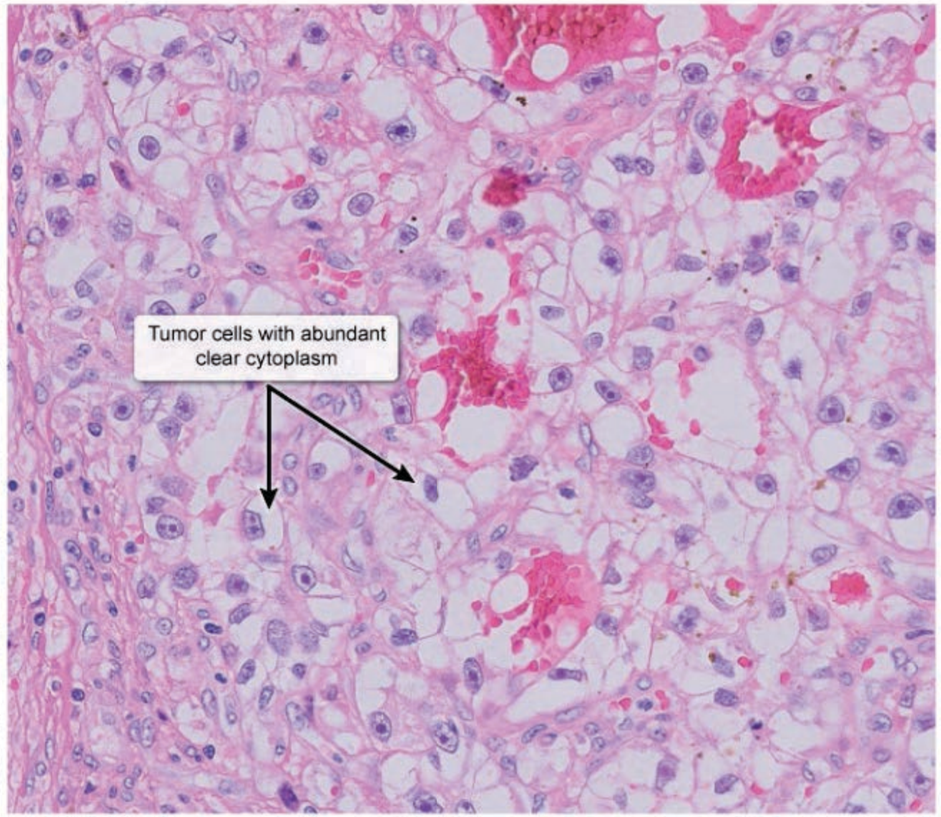
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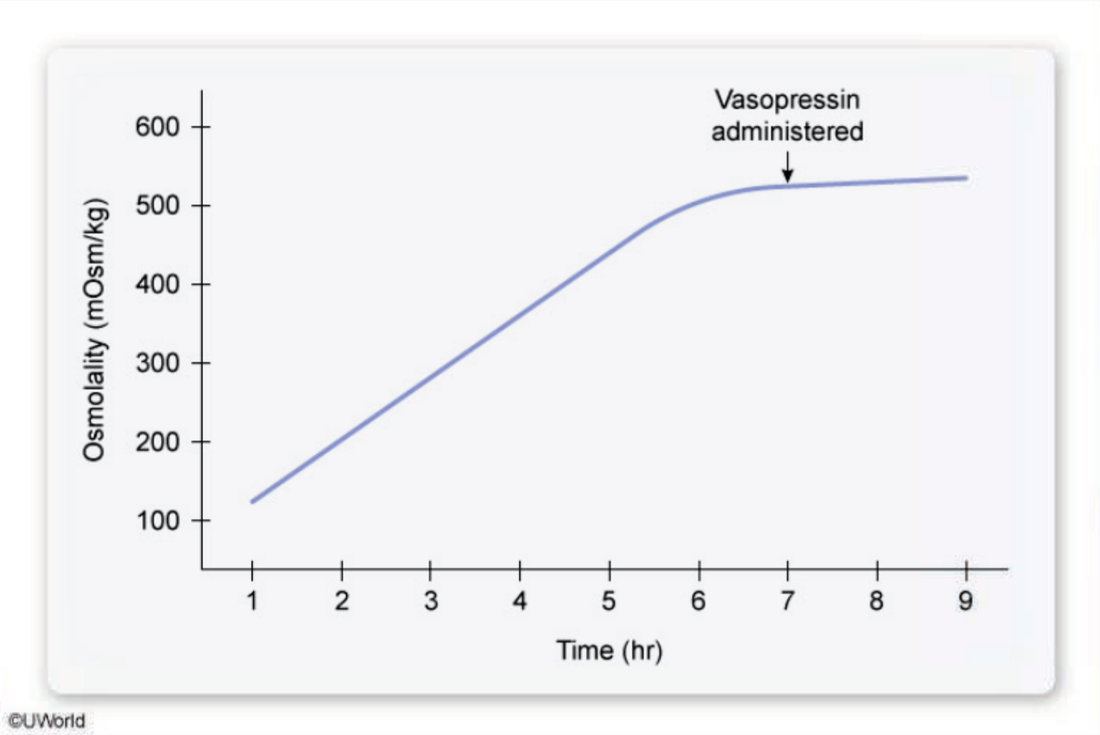
Clear cell renal cell carcinoma



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A 28-year-old woman comes to the clinic due to generalized weakness and frequent, high-volume urination. She has had no dysuria, hematuria, or abdominal pain. The patient's symptoms have been ongoing for several months, but she cannot recall exactly when they began. She has no other medical conditions. The patient is a single mother of a 2-year-old child, has little social support, and occasionally uses alcohol and marijuana "to cope with the stress." Vital signs and physical examination are normal. Blood glucose is 95 mg/dL and serum sodium is 132 mEq/L. Urinalysis shows no white or red blood cells. During further evaluation, urine osmolality is serially measured while fluid intake is restricted; vasopressin is subsequently administered 7 hours into the test. The results are shown below.

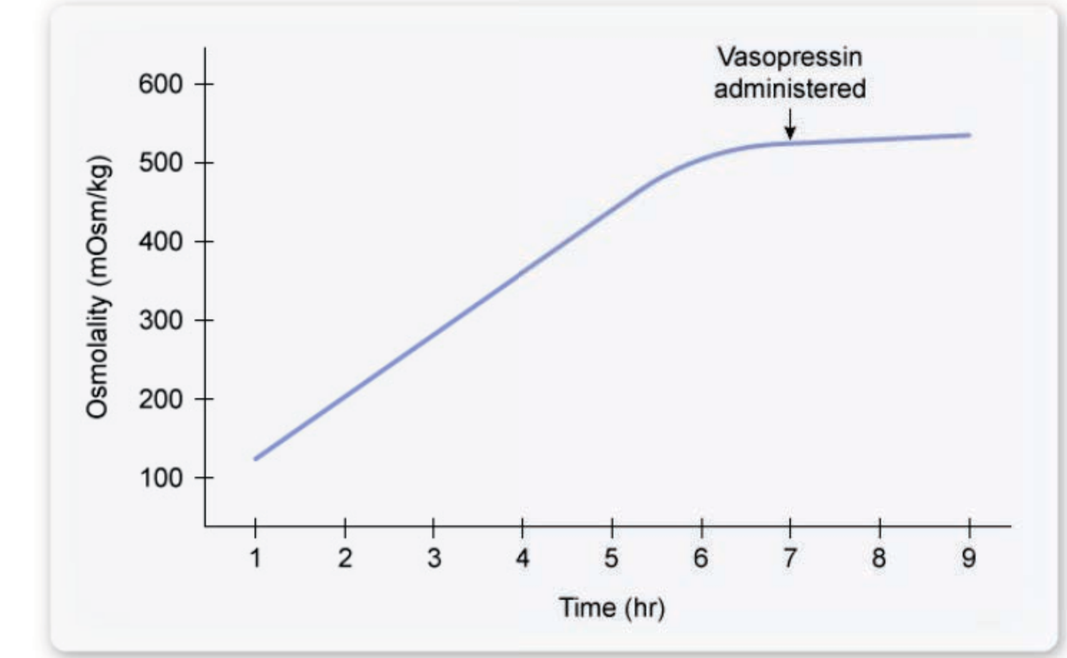


Which of the following is the most appropriate long-term treatment for this patient?

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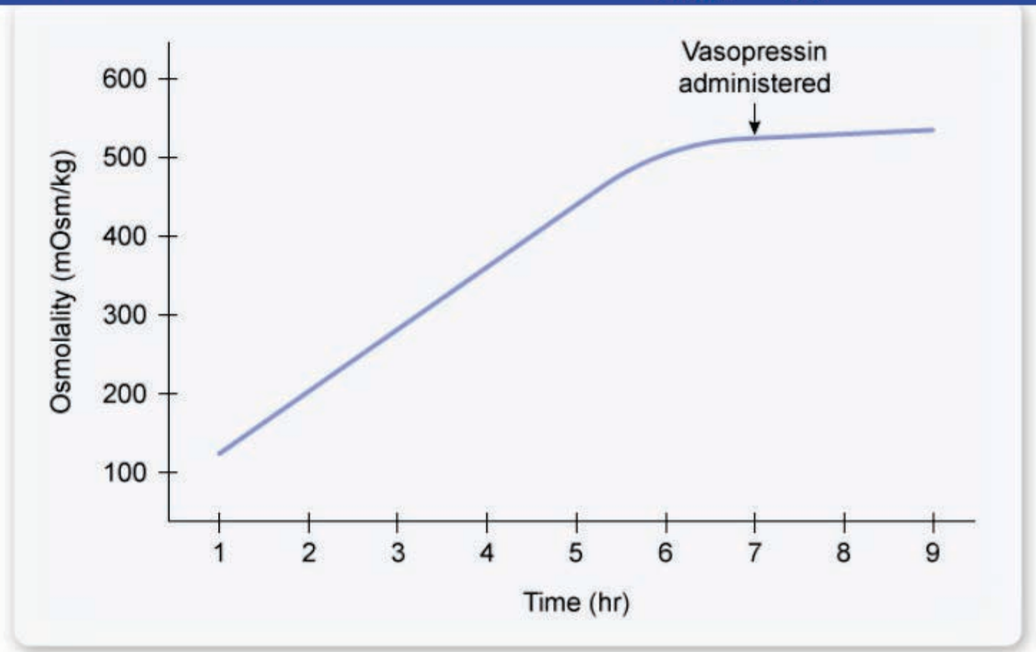


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Which of the following is the most appropriate long-term treatment for this patient?

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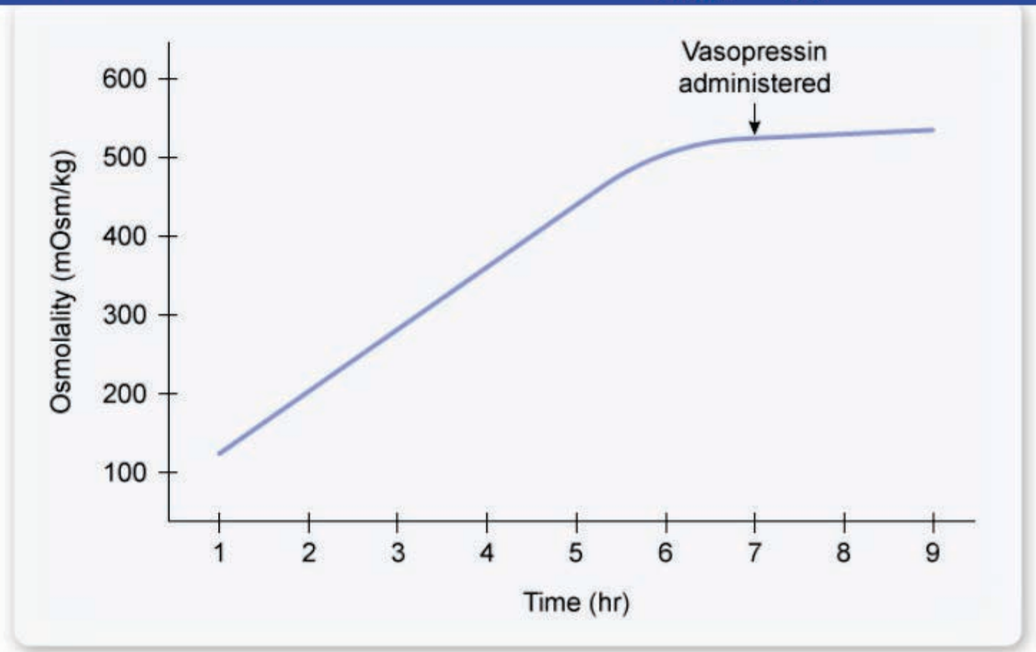
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Which of the following is the most appropriate long-term treatment for this patient?

- A. Desmopressin
- B. Hydrochlorothiazide
- C. Indomethacin
- D. Insulin
- E. Water restriction

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Which of the following is the most appropriate long-term treatment for this patient?

- A. Desmopressin (29%)
- ✗ B. Hydrochlorothiazide (13%)
- C. Indomethacin (3%)
- D. Insulin (1%)
- ✓ E. Water restriction (51%)

Incorrect
Correct answer
E

51%
Answered correctly

13 secs
Time Spent

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Polyuria & polydipsia			
		Water deprivation test	
	Serum sodium	Urine osmolality after water deprivation	Urine osmolality with vasopressin injection
Normal	Normal	Increased	No additional increase
Central diabetes insipidus	High	No change or mild increase	Large increase
Nephrogenic diabetes insipidus	High	No change or mild increase	Mild increase
Primary polydipsia	Low	Increased	No additional increase

This patient has **polyuria** (urine output >3 L/day) with a **low initial urine osmolality**, which is indicative of **water diuresis** caused by one of the following conditions:

- Diabetes insipidus (DI), which occurs due to either deficient antidiuretic hormone (ADH) production (central DI) or lack of renal response to ADH (nephrogenic DI)
- Primary polydipsia, which results from excessive water consumption (most common in patients with underlying psychiatric disease or emotional distress)

In patients with **primary polydipsia**, excessive water intake often leads to mild **hyponatremia**. In contrast, primary ADH deficiency in DI leads to free water loss often with ensuing hypernatremia. In certain patients, water deprivation testing may be helpful for differentiating PP from DI.

During a **water deprivation test**, drinking water is withheld and urine osmolality is monitored until it reaches a steady-state plateau (representing the maximal concentrating ability of the kidneys). Water deprivation in patients

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This patient has **polyuria** (urine output >3 L/day) with a **low initial urine osmolality**, which is indicative of **water diuresis** caused by one of the following conditions:

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During a **water deprivation test**, drinking water is withheld and urine osmolality is monitored until it reaches a steady-state plateau (representing the maximal concentrating ability of the kidneys). Water deprivation in patients with PP stimulates ADH secretion and leads to a significant **rise in urine concentration**, whereas urine in patients with DI remains dilute. Once a plateau is reached, **vasopressin is administered**. In DI, exogenous vasopressin causes an increase in urine osmolality; in PP, urine **concentration remains unchanged** because at this point in the test, the endogenous ADH effect is already at maximum.

If PP is confirmed, long-term management includes **restriction of free water** intake.

(Choices A, B, and C) Central DI can be treated with desmopressin (synthetic ADH analog), while nephrogenic DI is typically treated with thiazide diuretics (induce mild hypovolemia that decreases polyuria) or NSAIDs (inhibit renal prostaglandins that act as ADH antagonists). However, during water deprivation, patients with central or nephrogenic DI typically have no change or only a mild increase in urine osmolality due to lack of adequate ADH effect; subsequent vasopressin administration would also be expected to cause an increase in urine osmolality.

(Choice D) Severe hyperglycemia in diabetes mellitus can overwhelm the ability of the kidneys to recover the filtered glucose load, leading to osmotic diuresis and polyuria. However, this typically occurs with blood glucose

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underlying psychiatric disease or emotional distress)

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(Choice D) Severe hyperglycemia in diabetes mellitus can overwhelm the ability of the kidneys to recover the filtered glucose load, leading to osmotic diuresis and polyuria. However, this typically occurs with blood glucose >180 mg/dL; this patient's glucose is normal.

Educational objective:
Primary (psychogenic) polydipsia is characterized by excessive intake of free water, leading to hyponatremia and production of large volumes of dilute urine. Water restriction normalizes serum sodium levels and increases urine osmolality.

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A 72-year-old woman presents with difficulty hearing. She was admitted 1 week ago for dyspnea, orthopnea, and bilateral leg swelling which has been slowly improving with treatment. Her family members report that for the past 2 days, she has been turning her TV volume higher and they have to speak loudly for her to hear. Her hearing was normal prior to the hospitalization. Her medical problems include hypertension, heart failure, and chronic kidney disease. Examination shows moderate bilateral sensorineural hearing loss. Which of the following medications most likely contributed to this patient's hearing impairment?

- A. Carvedilol
- B. Digoxin
- C. Furosemide
- D. Hydrochlorothiazide
- E. Ramipril
- F. Spironolactone

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- A. Carvedilol (2%)
- ✗ B. Digoxin (12%)
- ✓ C. Furosemide (70%)
- D. Hydrochlorothiazide (6%)
- E. Ramipril (3%)
- F. Spironolactone (3%)

Incorrect
Correct answer
C

70%
Answered correctly

04 secs
Time Spent

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Explanation

This patient with pulmonary and peripheral edema due to heart failure and chronic kidney disease (CKD) was likely treated with diuretics during her hospitalization. **Loop diuretics** (eg, furosemide, torsemide, bumetanide), the most commonly used first line agents, work by **inhibiting Na/K/2Cl symporters** in the ascending limb of the loop of Henle. Inhibition of similar symporters in the inner ear is believed to cause **ototoxicity** (tinnitus, vertigo, hearing

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(Choice A) Carvedilol is a beta blocker with alpha blocking activity. Beta blockers are not initiated during decompensated heart failure as cardiac output is dependent on sympathetic input in this state. Major side effects include bradycardia, hypoglycemia, and fatigue.

(Choice B) Digoxin is used in certain patients with heart failure due to systolic dysfunction to help improve symptoms. Toxicity can cause cardiac arrhythmias, hyperkalemia, nausea, vomiting and confusion.

(Choice D) Hydrochlorothiazide is most often used for treating hypertension. Side effects of HCTZ include hypokalemia, hyponatremia and hypomagnesemia, and hypercalcemia.

(Choice E) Ramipril is an angiotensin converting enzyme inhibitor that is used in the treatment of hypertension and is beneficial in patients with heart failure. Side effects include cough, hyperkalemia and, less frequently, angioedema and anaphylactoid reactions.

(Choice F) Spironolactone works by antagonizing the effects of aldosterone in the distal tubule and collecting duct. Common side effects include hyperkalemia, gynecomastia, impotence, and decreased libido.

Educational objective:
Ototoxicity secondary to loop diuretics usually occurs with higher dosages, pre-existing chronic renal disease, rapid intravenous administration, or when used in combination with other ototoxic agents (aminoglycosides, salicylates, and cisplatin). Hearing impairment is usually reversible but may be permanent in some cases.

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A 56-year-old man with chronic renal insufficiency due to polycystic kidney disease is evaluated for placement of an arteriovenous fistula for dialysis access. Blood pressure is 140/90 mm Hg and pulse is 80/min. Examination shows 2+ bilateral edema of the lower extremities. Estimated glomerular filtration rate is 15 mL/min/1.73 m^2. Which of the following sets of laboratory findings is most likely in this patient?

	Parathyroid hormone	Serum calcium	Serum phosphorus	25-hydroxyvitamin D	1,25-dihydroxyvitamin D
○ A.	↑	↓	↑	Normal	↓
○ B.	↑	↑	↓	Normal	↑
○ C.	↓	↓	↑	Normal	↓
○ D.	↑	↓	↓	↓	↓
○ E.	↓	↑	↑	Normal	↑

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	Parathyroid hormone	Serum calcium	Serum phosphorus	25-hydroxyvitamin D	1,25-dihydroxyvitamin D	
✓ A.	↑	↓	↑	Normal	↓	(83%)
✗ B.	↑	↑	↓	Normal	↑	(3%)
C.	↓	↓	↑	Normal	↓	(4%)
D.	↑	↓	↓	↓	↓	(7%)
E.	↓	↑	↑	Normal	↑	(1%)

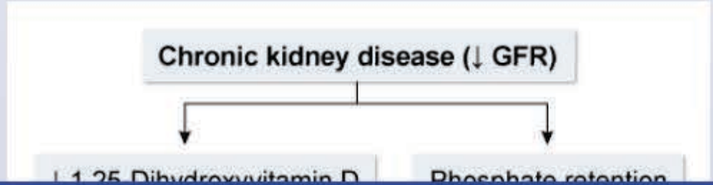
Incorrect
Correct answer
A

83%
Answered correctly

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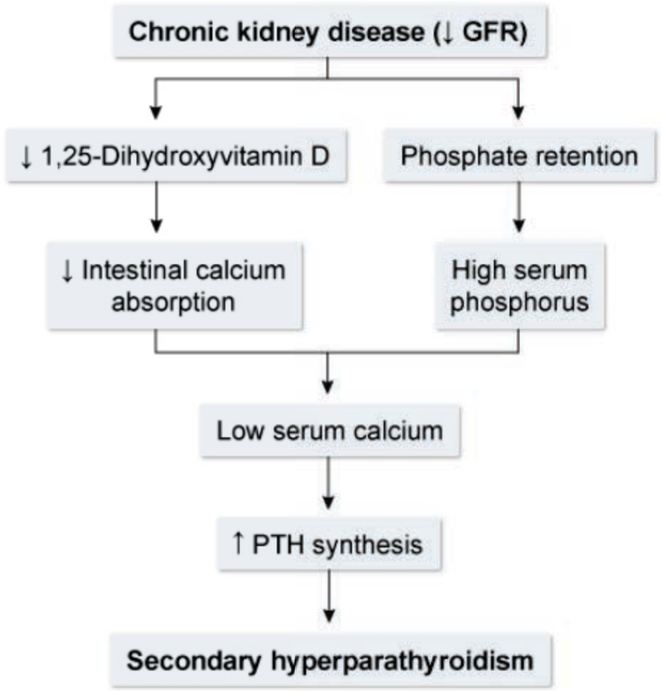
Explanation



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C. ↓ ↓ ↑ Normal ↓ (4%)

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GFR = glomerular filtration rate; **PTH** = parathyroid hormone.

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This patient has advanced **chronic kidney disease** (CKD). CKD can cause **hyperphosphatemia** due to the impaired ability of the kidneys to excrete phosphorus (particularly when GFR is <20 mL/min/1.73 m^2). Elevated blood phosphate triggers the release of fibroblast growth factor 23 from bone, which **lowers calcitriol** (1,25-dihydroxyvitamin D) production and intestinal calcium absorption. In addition, patients with advanced CKD typically have decreased renal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (the more active form) because of inadequate function of renal tissue. The resulting **hypocalcemia**, along with hyperphosphatemia, stimulates the secretion of parathyroid hormone (PTH) and leads to **secondary hyperparathyroidism**.

(Choice B) Primary hyperparathyroidism is characterized by hypercalcemia, hypophosphatemia (due to increased renal excretion of phosphorus), and increased renal production of 1,25-dihydroxyvitamin D. In secondary hyperparathyroidism due to CKD, PTH is high but serum phosphate is elevated and hypercalcemia would not be seen.

(Choice C) Hypoparathyroidism is characterized by hypocalcemia, hyperphosphatemia, and decreased renal production of 1,25-dihydroxyvitamin D. Hypoparathyroidism is usually caused by autoimmune disease or iatrogenic injury to the parathyroid glands during neck surgery.

(Choice D) Vitamin D deficiency (ie, low 25-hydroxyvitamin D) causes decreased absorption of dietary calcium and leads to hypocalcemia. The resulting increase in PTH (secondary hyperparathyroidism) causes decreased renal reabsorption of phosphate, leading to hypophosphatemia. 1,25-Dihydroxyvitamin D levels are typically low, although the increased renal conversion due to PTH may restore levels to within laboratory norms.

(Choice E) Elevated 1,25-dihydroxyvitamin D levels can be seen in granulomatous diseases (eg, sarcoidosis) and in excess intake of calcitriol supplements, and lead to increased intestinal absorption of calcium and phosphate (with hypercalcemia and hyperphosphatemia) and suppression of PTH.

Educational objective:

Chronic kidney disease can cause hyperphosphatemia due to impaired renal excretion of phosphorus. Elevated

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blood phosphate triggers the release of fibroblast growth factor 23 from bone, which **lowers calcitriol** (1,25-dihydroxyvitamin D) production and intestinal calcium absorption. In addition, patients with advanced CKD typically have decreased renal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (the more active form) because of inadequate function of renal tissue. The resulting **hypocalcemia**, along with hyperphosphatemia, stimulates the secretion of parathyroid hormone (PTH) and leads to **secondary hyperparathyroidism**.

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Educational objective:
Chronic kidney disease can cause hyperphosphatemia due to impaired renal excretion of phosphorus. Elevated blood phosphate triggers the release of fibroblast growth factor 23, which lowers calcitriol production and intestinal calcium absorption. The resulting hypocalcemia, along with hyperphosphatemia, leads to secondary hyperparathyroidism.

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A 20-year-old woman comes to the office due to gross hematuria. She otherwise feels well and has had no recent illnesses. She had a prior episode of hematuria 2 years ago that resolved spontaneously. The patient was diagnosed with type 1 diabetes mellitus approximately a year ago and is taking daily insulin injections. She works in a day care center and does not use tobacco, alcohol, or illicit drugs. Temperature is 37 C (98.6 F), blood pressure is 120/80 mm Hg, and pulse is 80/min. Physical examination shows no abnormalities. Laboratory results are as follows:

Serum creatinine	1.0 mg/dL
Serum albumin	4.0 g/dL
Urinalysis	numerous RBCs and few RBC casts; 1+ protein
Serum complement	normal

Which of the following is the most likely diagnosis?

- A. Diabetic nephropathy
- B. IgA nephropathy
- C. Membranous nephropathy
- D. Minimal change disease
- E. Poststreptococcal glomerulonephritis

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Serum creatinine	1.0 mg/dL
Serum albumin	4.0 g/dL
Urinalysis	numerous RBCs and few RBC casts; 1+ protein
Serum complement	normal

Which of the following is the most likely diagnosis?

- A. Diabetic nephropathy (16%)
- ✓ B. IgA nephropathy (55%)
- C. Membranous nephropathy (12%)
- D. Minimal change disease (5%)
- E. Poststreptococcal glomerulonephritis (9%)

Correct

55% Answered correctly

04 secs Time Spent

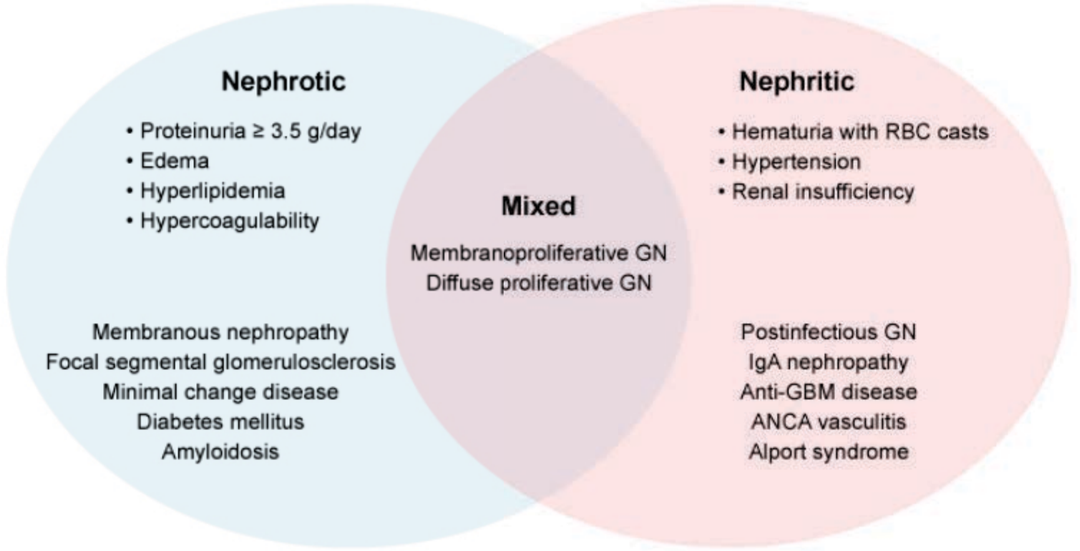
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Explanation

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Exhibit Display

Nephrotic vs. nephritic syndrome



ANCA = antineutrophilic cytoplasmic antibody; **GBM** = glomerular basement membrane; **GN** = glomerulonephritis; **RBC** = red blood cell.

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This patient has **nephritic syndrome** (ie, glomerulonephritis), which is characterized by **glomerular inflammation** resulting in **hematuria** and **red blood cell casts** on urinalysis. Patients may also have mild to

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This patient has **nephritic syndrome** (ie, glomerulonephritis), which is characterized by **glomerular inflammation**, resulting in **hematuria** and **red blood cell casts** on urinalysis. Patients may also have mild to moderate proteinuria, although typically less severe than in nephrotic syndrome. Acute kidney injury and hypertension may also be present.

The most common cause of nephritic syndrome is **immune complex deposition**. Most immune complex–related nephritic syndromes (eg, poststreptococcal or membranoproliferative glomerulonephritis, lupus nephritis) are associated with IgG and/or IgM complexes and have heavy glomerular complement deposition and subsequent serum hypocomplementemia (consumption). However, **IgA nephropathy** is characterized by **normal serum complement levels**, as seen in this patient, likely due to the weak complement-fixing activity of IgA compared to that of IgG and IgM.

IgA nephropathy typically presents with gross, often **recurrent**, hematuria, as in this case. Although this condition classically presents within several **days of an upper respiratory infection** (synpharyngitic hematuria), a high degree of suspicion must be maintained because episodes may also be **spontaneous**, as in this patient.

(Choices A, C, and D) Nephrotic syndromes cause heavy proteinuria, resulting in low albumin levels and edema; hematuria and red blood cell casts are typically absent. Etiologies include diabetic nephropathy, membranous nephropathy, and minimal change disease. Diabetic nephropathy typically takes >5 years to develop in type 1 diabetes, although it can be present at the time of diagnosis in patients with type 2 diabetes.

(Choice E) Poststreptococcal glomerulonephritis, which is most common in school-aged children, presents with nephritic syndrome several weeks after infection with group A *Streptococcus* (eg, pharyngitis, impetigo). This patient has had no recent illnesses, and in contrast to IgA nephropathy, hypocomplementemia would be expected in poststreptococcal glomerulonephritis.

Educational objective:
IgA nephropathy is characterized as recurrent hematuria that occurs spontaneously or within a few days of upper respiratory or pharyngeal infection (synpharyngitic hematuria). Unlike other causes of immune complex–mediated

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hypertension may also be present.

The most common cause of nephritic syndrome is **immune complex deposition**. Most immune complex–related nephritic syndromes (eg, poststreptococcal or membranoproliferative glomerulonephritis, lupus nephritis) are associated with IgG and/or IgM complexes and have heavy glomerular complement deposition and subsequent serum hypocomplementemia (consumption). However, **IgA nephropathy** is characterized by **normal serum complement levels**, as seen in this patient, likely due to the weak complement-fixing activity of IgA compared to that of IgG and IgM.

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(Choices A, C, and D) Nephrotic syndromes cause heavy proteinuria, resulting in low albumin levels and edema; hematuria and red blood cell casts are typically absent. Etiologies include diabetic nephropathy, membranous nephropathy, and minimal change disease. Diabetic nephropathy typically takes >5 years to develop in type 1 diabetes, although it can be present at the time of diagnosis in patients with type 2 diabetes.

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Educational objective:
IgA nephropathy is characterized as recurrent hematuria that occurs spontaneously or within a few days of upper respiratory or pharyngeal infection (synpharyngitic hematuria). Unlike other causes of immune complex–mediated nephritic syndromes (eg, poststreptococcal glomerulonephritis), IgA nephropathy is associated with normal serum complement levels.

References

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A 44-year-old man is brought to the emergency department with fatigue, shortness of breath, and lethargy. The patient had a brief upper respiratory illness about a month ago but began experiencing progressive dyspnea on exertion 2 weeks ago. He has no significant medical history and takes no medications. Blood pressure is 100/70 mm Hg and pulse is 95/min and regular. The apical impulse is palpated in the sixth intercostal space along the left anterior axillary line. An S3 is heard on cardiac auscultation. Bibasilar crackles are present. Distal extremities are cold, and there is 1+ peripheral edema. Laboratory results are as follows:

Blood urea nitrogen	45 mg/dL
Serum creatinine	1.8 mg/dL
Urine microscopy	
Red blood cells	0/hpf
White blood cells	0-1/hpf
Sediment	none

Which of the following is most likely to be present in this patient compared to the normal state?

- A. Decreased distal tubule sodium reabsorption
- B. Decreased proximal tubule urea reabsorption
- C. Decreased renal venous pressure
- D. Increased collecting duct free water excretion
- E. Increased proximal tubular sodium reabsorption
- F. Increased renal blood flow

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patient had a brief upper respiratory illness about a month ago but began experiencing progressive dyspnea on exertion 2 weeks ago. He has no significant medical history and takes no medications. Blood pressure is 100/70 mm Hg and pulse is 95/min and regular. The apical impulse is palpated in the sixth intercostal space along the left anterior axillary line. An S3 is heard on cardiac auscultation. Bibasilar crackles are present. Distal extremities are cold, and there is 1+ peripheral edema. Laboratory results are as follows:

Blood urea nitrogen	45 mg/dL
Serum creatinine	1.8 mg/dL
Urine microscopy	
Red blood cells	0/hpf
White blood cells	0-1/hpf
Sediment	none

Which of the following is most likely to be present in this patient compared to the normal state?

- A. Decreased distal tubule sodium reabsorption (10%)
- ✗ B. Decreased proximal tubule urea reabsorption (9%)
- C. Decreased renal venous pressure (17%)
- D. Increased collecting duct free water excretion (6%)
- ✓ E. Increased proximal tubular sodium reabsorption (50%)
- F. Increased renal blood flow (5%)

Incorrect
Correct answer
E

50%
Answered correctly

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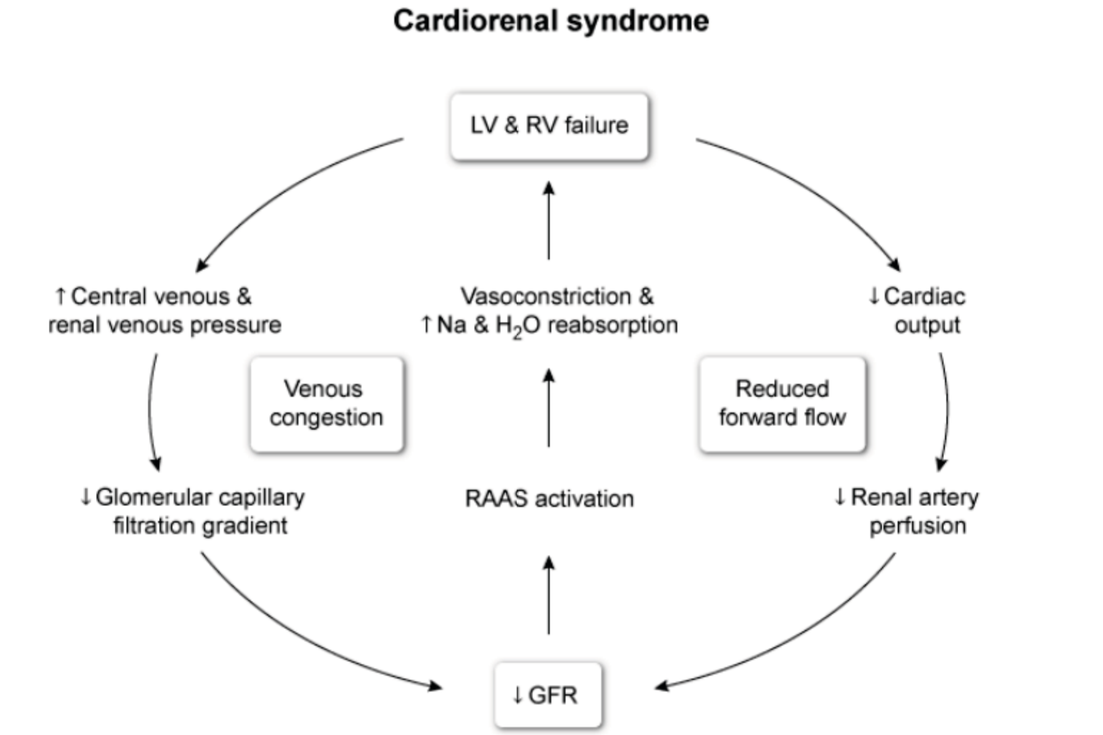
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GFR = glomerular filtration rate; **LV** = left ventricle; **RAAS** = renin-angiotensin-aldosterone system; **RV** = right ventricle.

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pres
myocarditis. The pathophysiology of DHF involves reduced cardiac output leading to **decreased renal blood**

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This patient with a recent upper respiratory infection has dyspnea, lower extremity edema, and an S3; this presentation suggests **decompensated heart failure** (DHF), likely due to dilated cardiomyopathy from viral myocarditis. The pathophysiology of DHF involves reduced cardiac output leading to **decreased renal blood flow**, which triggers neurohormonal adaptations that perpetuate a cycle of decompensation **(Choice F)**. These ultimately maladaptive neurohormonal changes include the following:

- Renin-angiotensin-aldosterone system (RAAS) activation, leading to **increased proximal tubular sodium reabsorption** (direct effect of angiotensin II)
- Antidiuretic hormone release, resulting in **increased free water reabsorption** in the collecting ducts
- Sympathetic nervous system activation, resulting in **systemic vasoconstriction**

In the short term, these adaptions increase blood volume and maintain systemic perfusion, allowing for a relatively normal glomerular filtration rate (GFR). However, over time, vasoconstriction-induced **increased afterload** and **ventricular overfilling** lead to decreased pump efficiency and decompensated failure. Renal dysfunction (eg, acute kidney injury) occurs in up to 60% of patients with DHF; it is often due to **cardiorenal syndrome**, a complication of the vicious cycle of DHF.

In cardiorenal syndrome, back pressure from the failing heart increases central venous and renal venous pressure **(Choice C)** to the point that the glomerular capillary filtration gradient drops substantially (due to interstitial edema causing increased hydrostatic pressure in Bowman capsule) and GFR significantly decreases. Characteristic laboratory findings in cardiorenal syndrome reflect **activation of the RAAS** and indicate a **prerenal** etiology, with low urine sodium (ie, fractional excretion of sodium <1%) and bland urine sediment. Urea passively follows sodium reabsorption in the proximal tubule, leading to an elevated **blood urea nitrogen/creatinine ratio** (>20:1).

(Choices A, B, and D) Decreased sodium and urea reabsorption and increased free water excretion are the normal responses to volume overload. However, in DHF, the appropriate response to volume overload is disrupted as the kidneys misinterpret reduced renal perfusion as an indicator of volume depletion (rather than volume

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- Renin-angiotensin-aldosterone system (RAAS) activation, leading to **increased proximal tubular sodium reabsorption** (direct effect of angiotensin II)
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(Choices A, B, and D) Decreased sodium and urea reabsorption and increased free water excretion are the normal responses to volume overload. However, in DHF, the appropriate response to volume overload is disrupted as the kidneys misinterpret reduced renal perfusion as an indicator of volume depletion (rather than volume overload) and activate RAAS and other maladaptive systems in response.

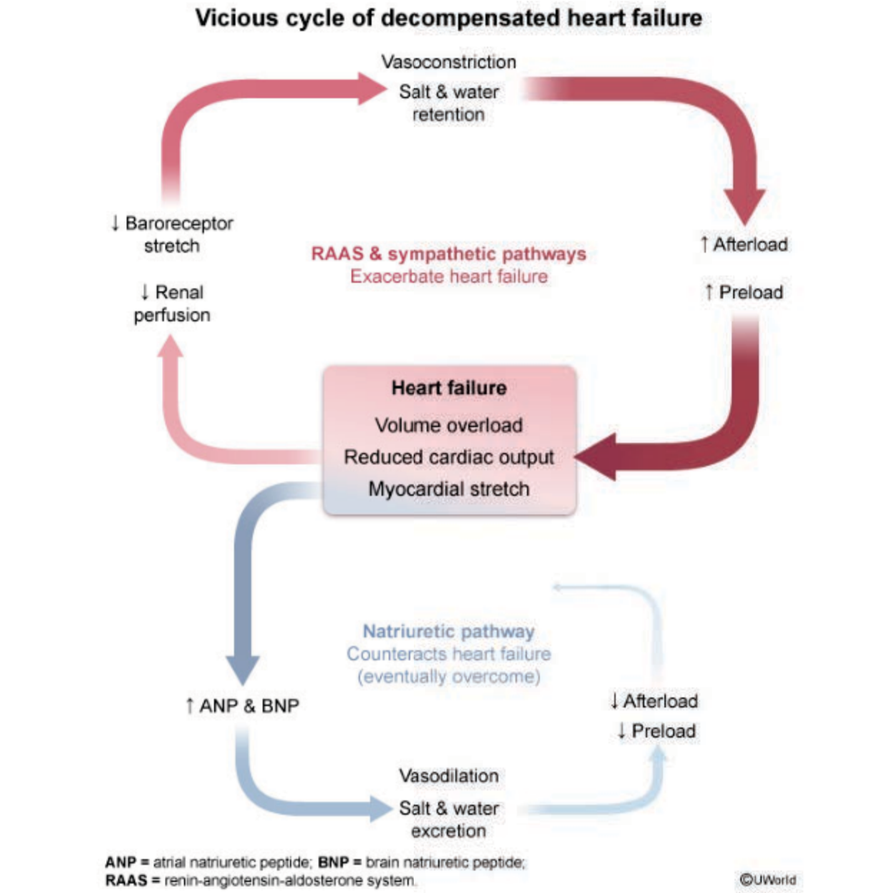
Educational objective:
Decompensated heart failure involves a vicious cycle of hemodynamic alterations and maladaptive neurohormonal changes resulting from decreased renal perfusion. Cardiorenal syndrome is a complication of this cycle, in which back pressure from the failing heart increases renal venous pressure to the point that the glomerular filtration rate drops substantially.

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causing increased hydrostatic pressure in Bowman capsule) and GFR significantly decreases. Characteristic

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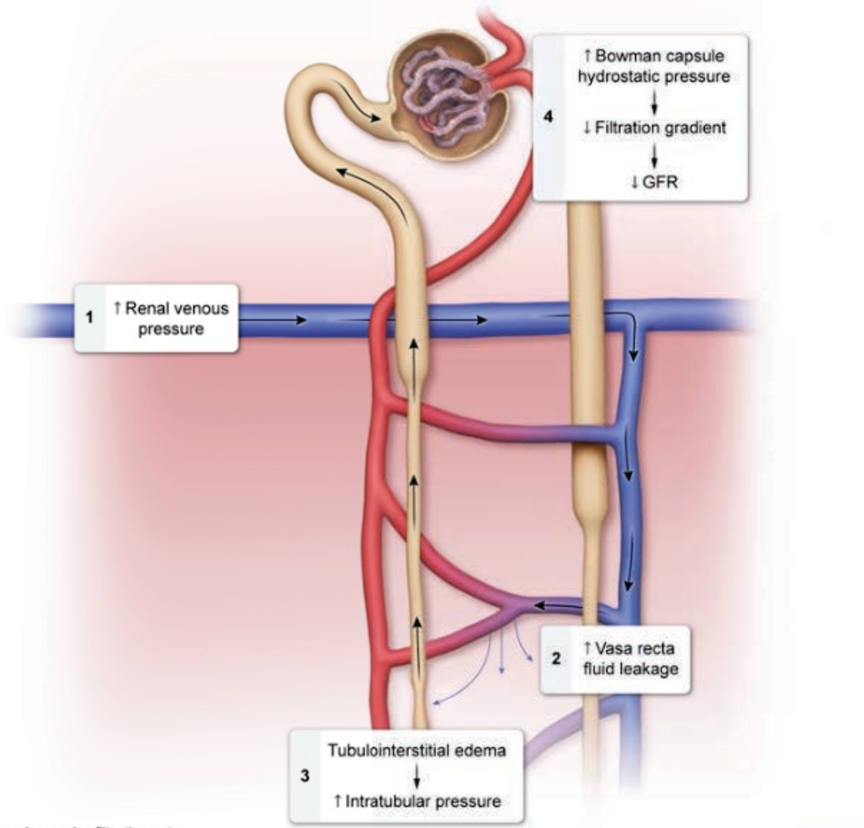
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as the kidneys misinterpret reduced renal perfusion as an indicator of volume depletion (rather than volume

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Renal venous congestion & acute kidney injury in cardiorenal syndrome



GFR = glomerular filtration rate.

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A 2-year-old girl is being evaluated for bilateral leg pain and muscle weakness with associated growth delay. She is able to sit but unable to stand or walk without support due to pain. Physical examination shows patchy alopecia, frontal bossing, wrist widening, and lateral bowing of the tibia and fibula. Skeletal imaging reveals generalized osteopenia with cupping and fraying at the metaphyseal ends of the long bones of the upper and lower extremities. Further evaluation reveals a homozygous inactivating mutation in the gene encoding the vitamin D receptor. A serum sample would most likely show which of the following findings?

	Calcium	Phosphorus	25-hydroxyvitamin D	1,25-dihydroxy vitamin D
○ A.	Decreased	Decreased	Decreased	Decreased
○ B.	Decreased	Decreased	Decreased	Normal
○ C.	Decreased	Decreased	Normal	Increased
○ D.	Increased	Decreased	Normal	Increased
○ E.	Increased	Increased	Normal	Increased

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		Calcium	Phosphorus	25-hydroxyvitamin D	1,25-dihydroxy vitamin D	
✗	A.	Decreased	Decreased	Decreased	Decreased	(27%)
	B.	Decreased	Decreased	Decreased	Normal	(6%)
✓	C.	Decreased	Decreased	Normal	Increased	(49%)
	D.	Increased	Decreased	Normal	Increased	(11%)
	E.	Increased	Increased	Normal	Increased	(4%)

Incorrect
Correct answer
C

49%
Answered correctly

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Explanation

This patient with bone pain and deformity (eg, frontal bossing, lower extremity bowing, abnormal mineralization of metaphyseal bone) has **rickets**. Dermal abnormalities (eg, alopecia) also are common due to keratinocyte dysfunction. The most common cause of rickets is vitamin D deficiency, but less common causes include

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Explanation

This patient with bone pain and deformity (eg, frontal bossing, lower extremity bowing, abnormal mineralization of metaphyseal bone) has **rickets**. Dermal abnormalities (eg, alopecia) also are common due to keratinocyte dysfunction. The most common cause of rickets is vitamin D deficiency, but less common causes include **hereditary vitamin D–resistant** rickets (HVDRR), which is caused by inactivating **mutations** of the vitamin D receptor.

Most vitamin D is stored in the form of 25-hydroxyvitamin D, which has only weak activity. In response to parathyroid hormone (PTH), it is converted to 1,25-dihydroxyvitamin D, the primary active form, by 1-alpha-hydroxylase in the kidneys. The action of 1,25-dihydroxyvitamin D is mediated by the vitamin D receptor; prominent effects include increases in intestinal calcium absorption, renal calcium and phosphate reabsorption, and bone mineralization.

In patients with HVDRR, as in those with severe nutritional vitamin D deficiency, **lack of vitamin D effect** leads to **hypocalcemia** (decreased intestinal absorption); the compensatory rise in PTH causes increased bone resorption and renal calcium reabsorption to partially correct the circulating calcium deficit but causes **renal phosphorus wasting** as well. The high levels of PTH also induce greater 1-alpha-hydroxylase activity, leading to **elevated 1,25-dihydroxyvitamin D** levels.

(Choice A) Catabolism of vitamin D is initiated by CYP24A1 (ie, 24-hydroxylase), which inactivates both the 25- and 1,25-hydroxylated vitamin D forms. Expression of this enzyme is induced by carbamazepine and other anticonvulsants (eg, phenytoin), increasing the risk of vitamin D deficiency.

(Choice B) Patients with vitamin D–deficiency rickets, the more common type, have clinical features resembling HVDRR, including hypocalcemia and hypophosphatemia. However, 25-hydroxyvitamin D is low, reflecting reduced whole-body stores (1,25-dihydroxyvitamin D may sometimes be normal due to upregulation of PTH).

(Choice D) Primary hyperparathyroidism presents with mild or moderate hypercalcemia. Serum phosphorus is

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(Choice B) Patients with vitamin D–deficiency rickets, the more common type, have clinical features resembling HVDRR, including hypocalcemia and hypophosphatemia. However, 25-hydroxyvitamin D is low, reflecting reduced whole-body stores (1,25-dihydroxyvitamin D may sometimes be normal due to upregulation of PTH).

(Choice D) Primary hyperparathyroidism presents with mild or moderate hypercalcemia. Serum phosphorus is low due to renal phosphate wasting, and 1,25-dihydroxyvitamin D is elevated due to increased activity of 1-alpha-hydroxylase. 25-hydroxyvitamin D levels are generally unaffected.

(Choice E) Granulomatous diseases (eg, sarcoidosis, tuberculosis) can be associated with extrarenal expression of 1-alpha-hydroxylase by macrophages. This leads to increased production of 1,25-dihydroxyvitamin D, hypercalcemia, and hyperphosphatemia. Total vitamin D stores (25-hydroxyvitamin D) are generally normal.

Educational objective:
Lack of vitamin D effect (eg, vitamin D deficiency, vitamin D receptor mutation) causes hypocalcemia due to inadequate calcium absorption. The compensatory rise in parathyroid hormone (PTH) causes increased bone resorption, renal calcium reabsorption, and renal phosphorus wasting. PTH also induces 1-alpha-hydroxylase activity, leading to elevated 1,25-dihydroxyvitamin D levels.

Biochemistry Renal, Urinary Systems & Electrolytes Vitamin D deficiency

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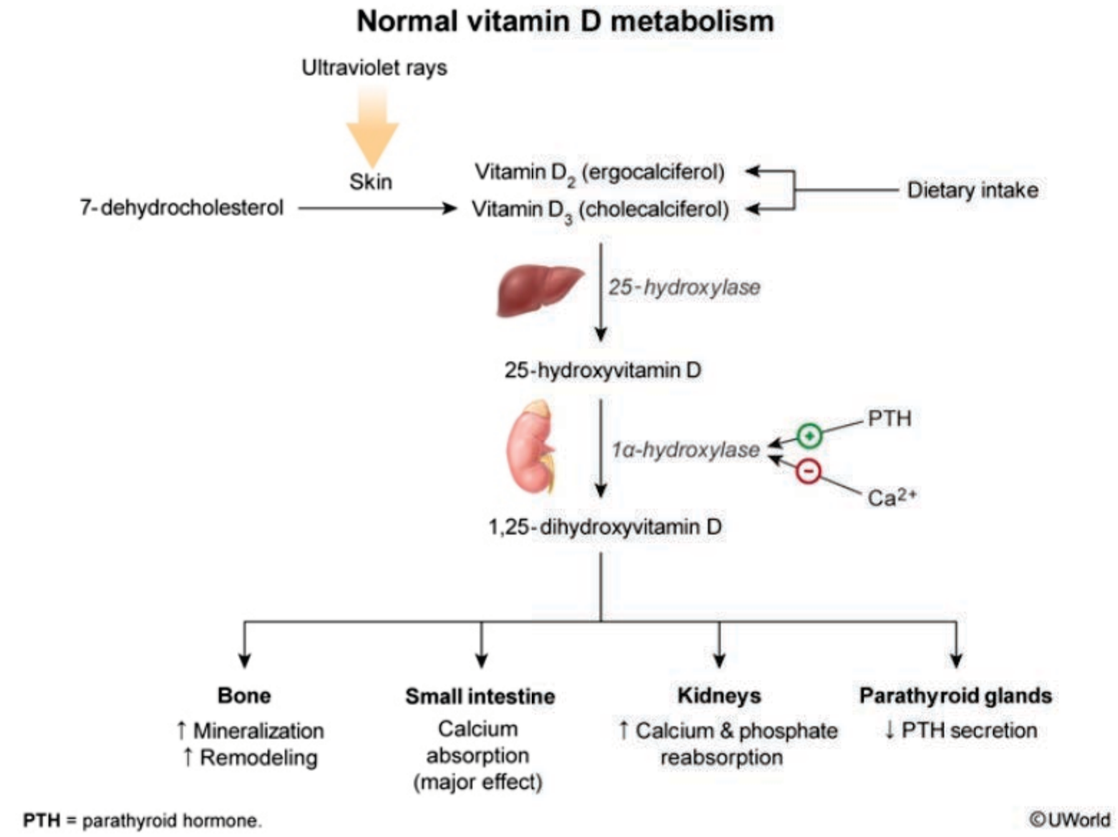
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Correct answer

49%
Answered correctly

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(Choice B) Patients with vitamin D–deficiency rickets, the more common type, have clinical features resembling

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A 21-year-old male presents to his physician after noticing that his urine had a "frothy" appearance. He also complains of easy fatigability and anorexia. His past medical history is significant only for an upper respiratory infection several weeks ago. Physical examination reveals symmetric pitting edema of the ankles. Which of the following is most likely decreased in this patient?

- A. Capillary hydrostatic pressure
- B. Interstitial fluid pressure
- C. Plasma oncotic pressure
- D. Tissue lymphatic drainage
- E. Circulating aldosterone level

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- A. Capillary hydrostatic pressure (5%)
- ✗ B. Interstitial fluid pressure (3%)
- ✓ C. Plasma oncotic pressure (83%)
- D. Tissue lymphatic drainage (5%)
- E. Circulating aldosterone level (1%)

Incorrect
Correct answer
C

83%
Answered correctly

03 secs
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Explanation

Frothy, foamy urine may be caused by proteinuria or bile salts in the urine. This patient's history of a recent upper respiratory infection and ankle edema on physical exam suggest a diagnosis of nephrotic syndrome with associated low serum albumin. Hypoalbuminemia lowers the plasma oncotic pressure and causes interstitial edema formation due to net plasma filtration. Minimal change disease (MCD) is the most common cause of nephrosis in children, and can occur in adults as well.

(Choice A) A decrease in capillary hydrostatic pressure would tend to decrease net plasma filtration and interstitial edema formation.

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(Choice A) A decrease in capillary hydrostatic pressure would tend to decrease net plasma filtration and interstitial edema formation.

(Choice B) This patient's ankle edema is the result of a transudate of plasma into the interstitial tissues of the ankle. We would therefore expect an increase in the steady state interstitial fluid pressure in the ankles.

(Choice D) While a primary decrease in lymphatic drainage can cause interstitial edema, the rate of lymphatic drainage would be increased in this particular patient because of the accumulation of ankle interstitial fluid.

(Choice E) In nephrotic syndrome, the plasma oncotic pressure is decreased, which causes net plasma filtration into the interstitium, thus decreasing the effective circulating intravascular volume. This reduction of the intravascular volume stimulates a compensatory increase in the activity of the renin-angiotensin-aldosterone system. Patients with nephrotic syndrome tend to have elevated circulating aldosterone levels.

Educational Objective:
Frothy or foamy urine may be caused by proteinuria. Heavy proteinuria, as in nephrotic syndrome, can cause regional or generalized interstitial edema because the decrease in serum albumin and total protein concentrations lowers the plasma oncotic pressure and increases net plasma filtration in capillary beds.

Pathophysiology	Renal, Urinary Systems & Electrolytes	Glomerular disorders
Subject	System	Topic

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A 55-year-old man is found unresponsive on the street during a cold winter night. He is hypothermic and does not follow commands. Medical history is unavailable. Despite rewarming efforts, the patient dies in the emergency department. An autopsy is performed. Light microscopy of a section of the patient's kidney is shown on the slide below.

This individual's renal condition could most likely have been prevented by use of which of the following types of medication?

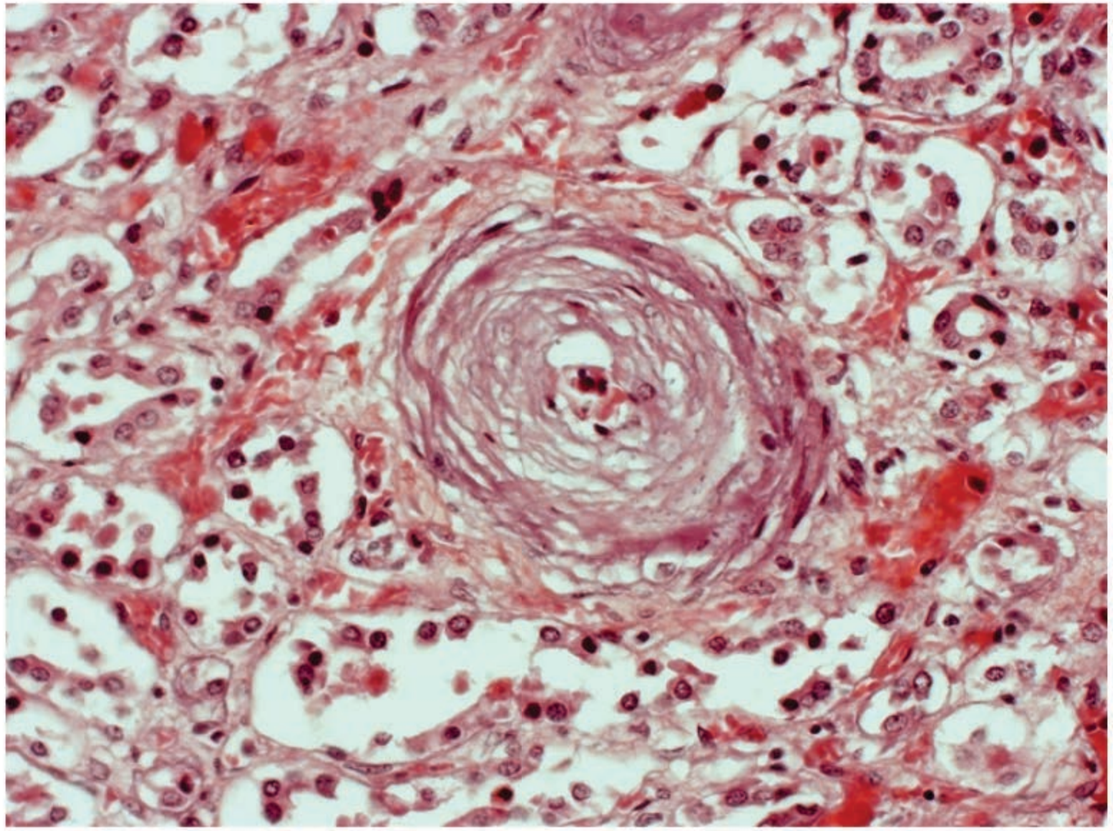
- A. Antibiotics
- B. Antihypertensives
- C. Antiplatelet agents
- D. Glucocorticoids
- E. Hypoglycemic agents
- F. Nonsteroidal anti-inflammatory drugs

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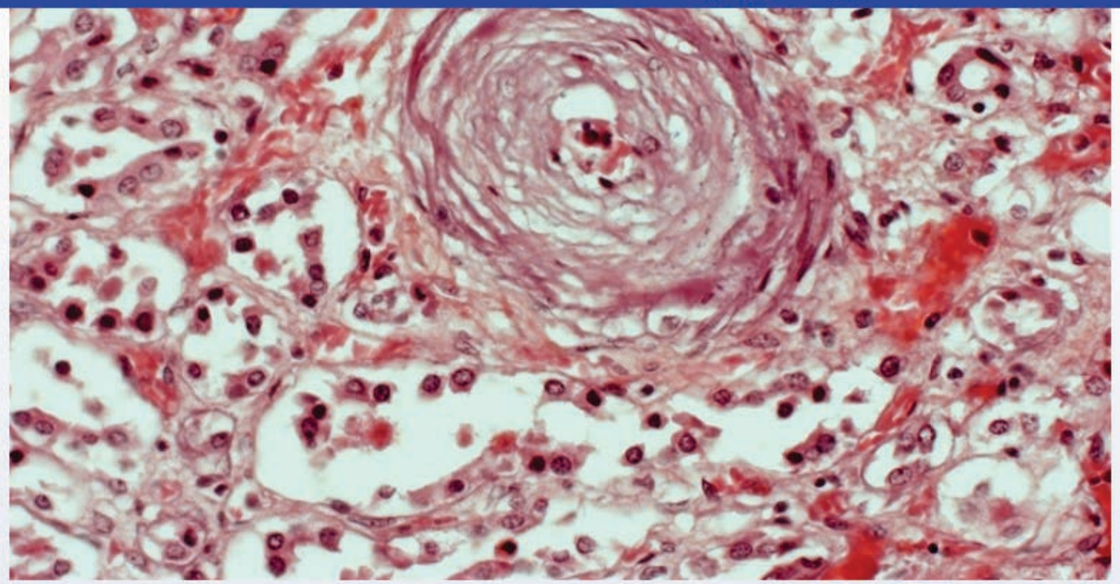
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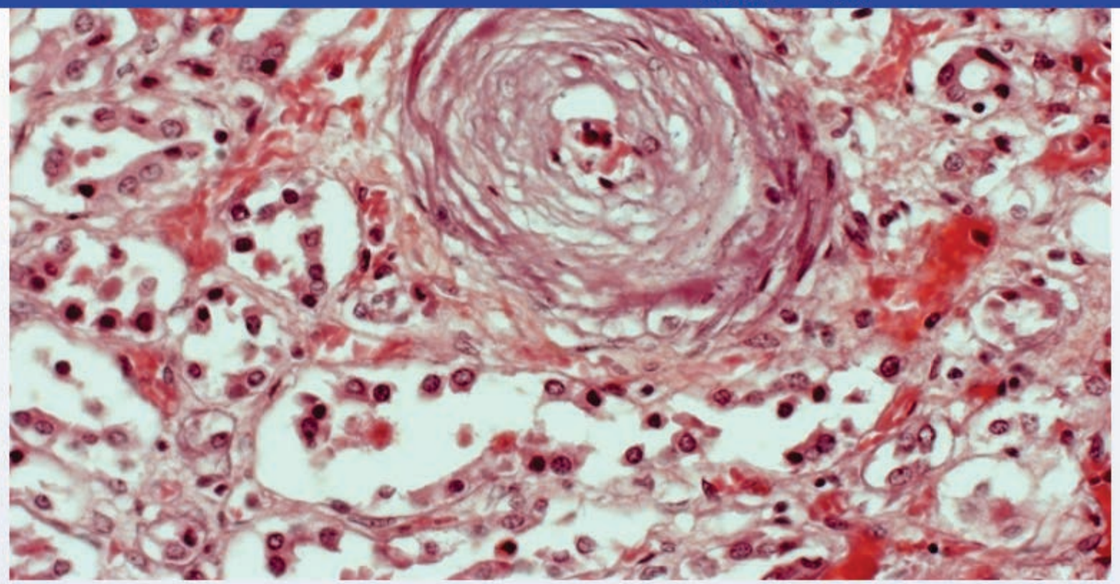


This individual's renal condition could most likely have been prevented by use of which of the following types of medication?

- A. Antibiotics
- B. Antihypertensives
- C. Antiplatelet agents
- D. Glucocorticoids
- E. Hypoglycemic agents
- F. Nonsteroidal anti-inflammatory drugs

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This individual's renal condition could most likely have been prevented by use of which of the following types of medication?

- A. Antibiotics (1%)
- ✓ B. Antihypertensives (82%)
- C. Antiplatelet agents (1%)
- D. Glucocorticoids (5%)
- E. Hypoglycemic agents (7%)
- F. Nonsteroidal anti-inflammatory drugs (1%)

Correct

82% Answered correctly

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Correct

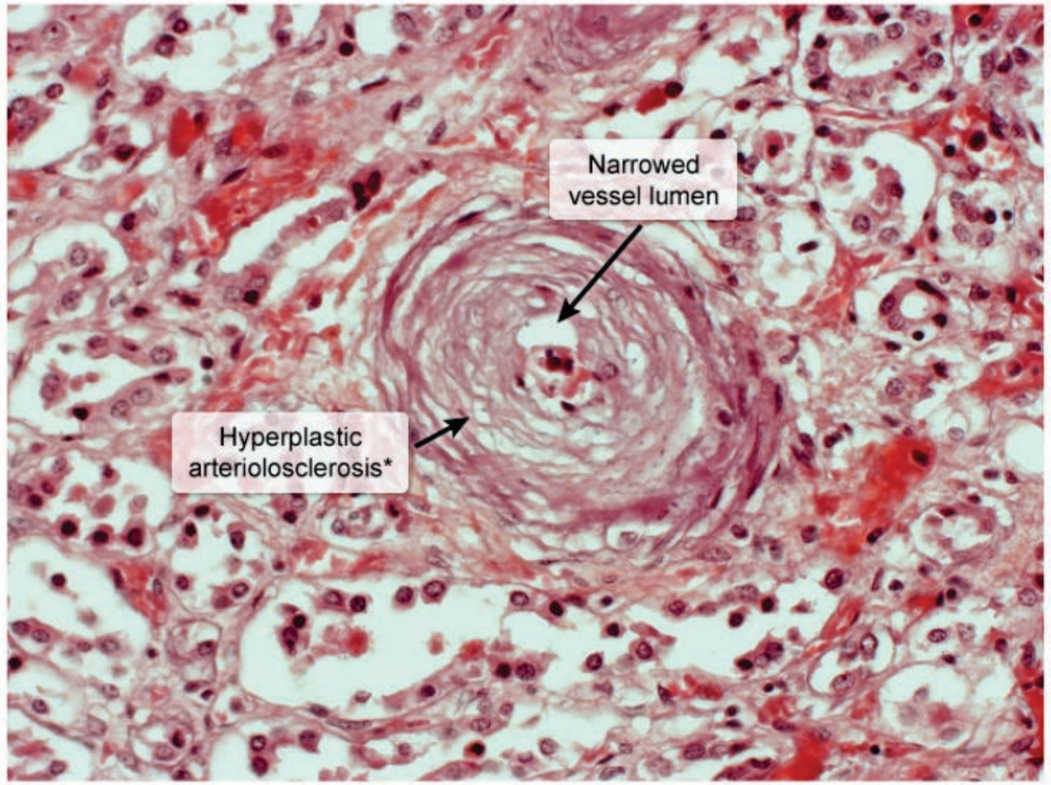
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Malignant nephrosclerosis



*Vessel wall thickened by concentric layers of collagen and smooth muscle ("onion-skinning")

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Hypertensive (malignant) nephrosclerosis is the renal manifestation of **hypertensive emergency**, a condition

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vessel wall thickened by concentric layers of collagen and smooth muscle ("onion-skinning")

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Hypertensive (malignant) nephrosclerosis is the renal manifestation of **hypertensive emergency**, a condition in which severe hypertension results in end-organ damage. Markedly elevated blood pressure causes vascular endothelial damage, leading to inflammation, cell necrosis, and extravasation of plasma proteins (eg, fibrinogen, coagulation factors). In the kidneys, this results in a characteristic set of histologic changes:

- Leakage of fibrinogen and coagulation factors through the damaged endothelium causes fibrin deposition in vessel walls, which appear as circumferential, acellular eosinophilic deposits **(fibrinoid necrosis)**.
- Over time, release of growth factors by damaged tissue stimulates the formation of concentric layers of collagen and proliferating smooth muscle cells, resulting in an "**onion skin**" appearance **(hyperplastic arteriosclerosis)** of the arteriole, as seen in this patient.

These processes result in narrowing and obliteration of the arteriolar lumens, reducing glomerular perfusion and filtration, with subsequent activation of the renin-angiotensin-aldosterone system. This maladaptation can result in a further increase in blood pressure and compromised circulation in other organs.

Treatment of hypertensive emergency includes **antihypertensive** therapy with the goal of lowering blood pressure to prevent end-organ damage.

(Choices A and E) Antibiotics and hypoglycemic agents are not used in the treatment of hypertensive emergency. Although sepsis can cause acute kidney injury and unresponsiveness, histology would show evidence of tubular necrosis with sloughing of tubular epithelial cells and loss of basement membrane integrity.

(Choice C) Antiplatelet agents would be useful if the endothelial dysfunction in hypertensive emergencies led to thrombotic complications (eg, acute myocardial infarction, acute ischemic stroke), but would not have any effect on preventing acute hypertensive nephrosclerosis.

(Choice D) The mineralocorticoid activity of steroids leads to salt and water retention, increasing blood pressure and worsening hypertension.

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(Choice D) The mineralocorticoid activity of steroids leads to salt and water retention, increasing blood pressure and worsening hypertension.

(Choice F) Nonsteroidal anti-inflammatory drugs inhibit prostaglandin secretion, resulting in vasoconstriction and decreased renal blood flow. This would worsen hypertension by activating the renin-angiotensin-aldosterone system.

Educational objective:
Hyperplastic arteriosclerosis ("onion-skinning") and fibrinoid necrosis of the renal arterioles are typical morphologic findings in hypertensive (malignant) nephrosclerosis. End-organ damage can be prevented by treatment of high blood pressure with antihypertensives.

Pathology Renal, Urinary Systems & Electrolytes Primary hypertension

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Hypertensive crisis	
Hypertensive urgency	• Severe hypertension (≥180/120 mm Hg) • No evidence of end-organ damage
Hypertensive emergency	• Severe hypertension with end-organ damage: ◦ Cardiovascular: angina, myocardial infarction, aortic dissection ◦ CNS: encephalopathy, cerebral infarct/hemorrhage ◦ Kidney: acute hypertensive nephrosclerosis ◦ Lung: pulmonary edema ◦ Retina: papilledema, flame-shaped hemorrhages, exudates

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A 38-year-old man is brought to the emergency department due to progressive nausea, confusion, and unsteady gait. Family members state that symptoms started 4 days ago after he went to the dentist due to a toothache, for which he was prescribed ibuprofen. He also takes lithium for bipolar disorder. On examination, he is drowsy and ataxic, having slurred speech and coarse tremors. His serum lithium level is 3.86 mEq/L (therapeutic range: 0.8-1.2 mEq/L), and serum creatinine and blood urea nitrogen are elevated. While in the emergency department, he develops a generalized tonic-clonic seizure. During emergent hemodialysis treatment, his blood is passed along a semipermeable membrane and allowed to equilibrate with a dialysate solution. Which of the following is most likely to increase the rate of drug removal?

- A. Adding lithium to the dialysis solution
- B. Decreasing dialysis solution temperature
- C. Decreasing the membrane pore size
- D. Increasing surface area of the membrane
- E. Increasing thickness of the membrane

Submit

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- A. Adding lithium to the dialysis solution (1%)
- ✗ B. Decreasing dialysis solution temperature (1%)
- C. Decreasing the membrane pore size (3%)
- ✓ D. Increasing surface area of the membrane (92%)
- E. Increasing thickness of the membrane (1%)

Incorrect
Correct answer
D

92%
Answered correctly

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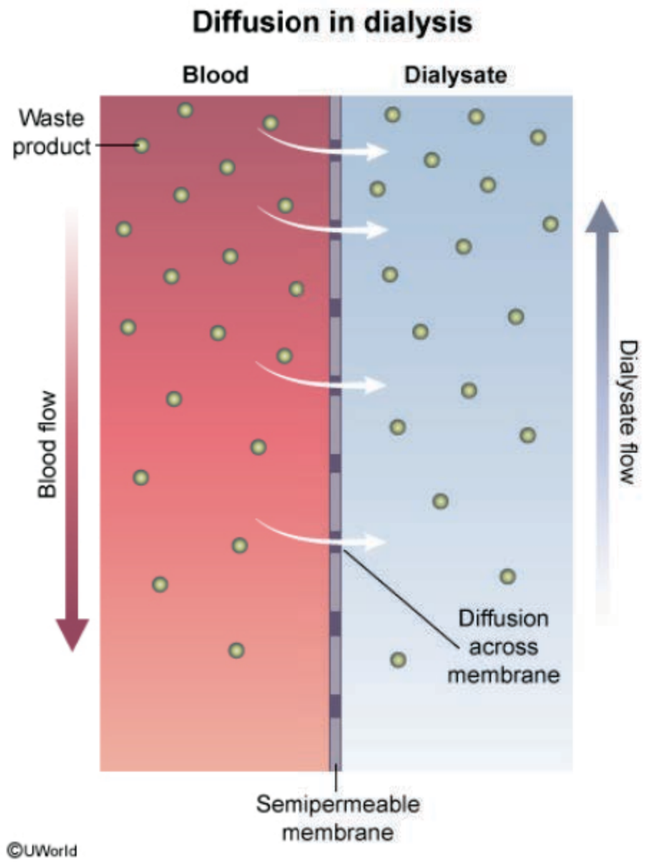
Explanation



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C. Decreasing the membrane pore size (3%)

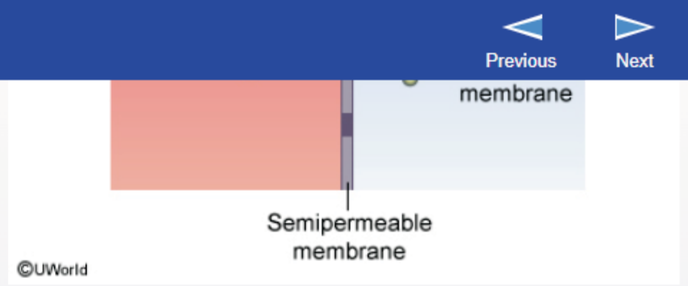
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membrane

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This patient is presenting with severe lithium toxicity secondary to his recent NSAID use and requires urgent hemodialysis to lower his blood lithium levels. Multiple factors affect the rate of **molecular diffusion** across a semipermeable membrane separating 2 well-mixed compartments. The number of molecules that cross the membrane per second is **proportional** to the molecular **concentration difference** across the membrane, the **surface area** of the membrane, and the solubility of the substance. Diffusion is inversely proportional to the total membrane thickness and the molecular weight of the molecule.

(Choice A) Adding lithium to the dialysate will decrease the concentration gradient between the dialysate and the patient's plasma. This would decrease the diffusion rate of lithium across the membrane.

(Choice B) Diffusion rate generally increases with temperature due to increased molecular movement speed and increased macromolecule solubility.

(Choices C and E) A decrease in membrane pore size would slow or prevent diffusion of larger molecules across the membrane. Increasing membrane thickness would also decrease diffusion rate.

Educational objective:
Diffusion speed across a semipermeable membrane increases with higher molecular concentration gradients, larger membrane surface areas, and increased solubility of the diffusing substance. Diffusion speed decreases with increased membrane thickness, smaller pore size, higher molecular weights, and lower temperatures.

Physiology	Renal, Urinary Systems & Electrolytes	Lithium
Subject	System	Topic

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membrane

Exhibit Display

Lithium toxicity	
Etiology	Acute toxicity • Intentional overdose Chronic toxicity • Decreased renal perfusion (↓ lithium clearance) ◦ Dehydration ◦ Thiazide diuretics, NSAIDs, ACE inhibitors
Clinical features	Acute toxicity • Gastrointestinal: nausea, vomiting, diarrhea • Late neurologic sequelae Chronic toxicity (neurologic) • Lethargy, confusion, agitation • Ataxia, tremor/fasciculations, seizure
Treatment	• Intravenous hydration • Hemodialysis (severe cases)
NSAID = nonsteroidal anti-inflammatory drug.	

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A 62-year-old man is brought to the emergency department by ambulance following a motor vehicle collision. The patient is obtunded but responds to painful stimuli. Blood pressure is 160/90 mm Hg, pulse is 50/min, and respirations are 10/min. Brain imaging reveals diffuse axonal injury and cerebral edema but no intracranial hematoma. Intravenous mannitol is administered to treat elevated intracranial pressure. Thirty minutes later, the patient has worsening tachypnea and hypoxemia. Chest x-ray shows new bilateral interstitial infiltrates. Which of the following is the most likely cause of this patient's respiratory distress?

- A. Direct medication-induced pulmonary toxicity
- B. Excessive antidiuretic hormone release
- C. IgE-mediated allergic drug reaction
- D. Rapid increase in intravascular volume
- E. Sudden decrease in intracranial pressure

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- A. Direct medication-induced pulmonary toxicity (10%)
- ✗ B. Excessive antidiuretic hormone release (6%)
- C. IgE-mediated allergic drug reaction (5%)
- ✓ D. Rapid increase in intravascular volume (57%)
- E. Sudden decrease in intracranial pressure (20%)

Incorrect
Correct answer
D

57%
Answered correctly

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Explanation

Traumatic brain injury can cause cerebral edema and increased intracranial pressure (ICP), which predisposes to cerebral hypoperfusion and herniation as the brain parenchyma expands within a fixed space. The increased ICP can be temporarily reduced with intravenous **mannitol**, an osmotically active agent that quickly **raises plasma osmolality** and therefore plasma oncotic pressure. This draws water from the interstitial space into the vascular compartment, **reducing ICP** but at the expense of a rapid increase in intravascular volume.

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Most patients can tolerate the rapid **increase in intravascular volume**, but those with a history of heart failure and elderly patients with a low reserve of left ventricular function are at risk for complications that include **pulmonary edema**. Pulmonary edema can occur due to an abrupt increase in pulmonary capillary hydrostatic pressure due to the heart's inability to maintain forward flow. Clinical manifestations include **respiratory distress** (eg, tachypnea) and hypoxemia; chest x-ray typically shows **bilateral infiltrates** in the interstitium and/or alveoli.

(Choice A) Although direct medication-induced pulmonary toxicity can cause pulmonary edema, this is not typically seen with mannitol. Direct pulmonary toxicity is more common with nitrofurantoin, amiodarone, methotrexate, and some chemotherapeutic agents (eg, bleomycin, busulfan).

(Choice B) Excessive antidiuretic hormone (ADH) release from the pituitary gland—which can occur in the setting of traumatic brain injury—leads to free water retention and hyponatremia. Pulmonary edema does not occur as patients remain euvolemic.

(Choice C) IgE-mediated allergic drug reactions (ie, anaphylaxis) can lead to respiratory distress (eg, tachypnea, hypoxia) due to upper airway closure, bronchospasm, and pulmonary edema. However, hypersensitivity to mannitol would be unusual; respiratory distress following mannitol administration is far more likely to be due to the subsequent increase in intravascular volume.

(Choice E) Although this patient has likely experienced a sudden decrease in ICP due to the intended effect of intravenous mannitol, this would not directly explain the respiratory distress.

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compartment, **reducing ICP** but at the expense of a rapid increase in intravascular volume.

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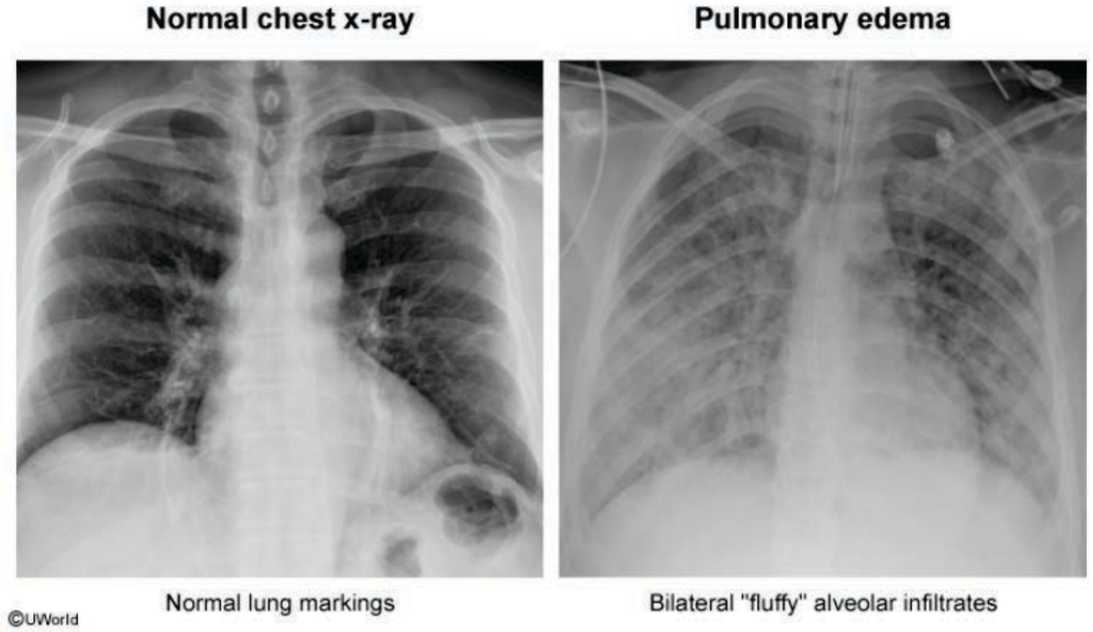
(Choice E) Although this patient has likely experienced a sudden decrease in ICP due to the intended effect of intravenous mannitol, this would not directly explain the respiratory distress.

Educational objective:
Intracranial pressure can be temporarily reduced with intravenous mannitol, an osmotically active agent that increases plasma oncotic pressure, causing water from the interstitial space to be drawn into the vascular compartment. In some patients (eg, history of heart failure, low left ventricular reserve function), rapidly increased intravascular volume can cause pulmonary edema by abruptly increasing pulmonary capillary hydrostatic pressure.

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Explanation

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A healthy 32-year-old man enrolls in a clinical study investigating potassium handling by the kidney. During the study period, he is given oral potassium supplements and potassium levels in the serum and urine are closely monitored. Compared to the amount of potassium delivered to the glomerular capillaries, the percentage of potassium remaining in this individual's tubular fluid is most likely to vary by which of the following amounts?

	Bowman's capsule	End of proximal tubule	End of thick ascending limb of Henle's loop	End of collecting duct
○ A.	100%	35%	10%	110%
○ B.	100%	35%	70%	110%
○ C.	75%	50%	25%	110%
○ D.	100%	50%	100%	110%

Submit

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	Bowman's capsule	End of proximal tubule	End of thick ascending limb of Henle's loop	End of collecting duct	
✓ A.	100%	35%	10%	110%	(56%)
✗ B.	100%	35%	70%	110%	(29%)
C.	75%	50%	25%	110%	(6%)
D.	100%	50%	100%	110%	(7%)

Incorrect
Correct answer
A

56%
Answered correctly

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Explanation

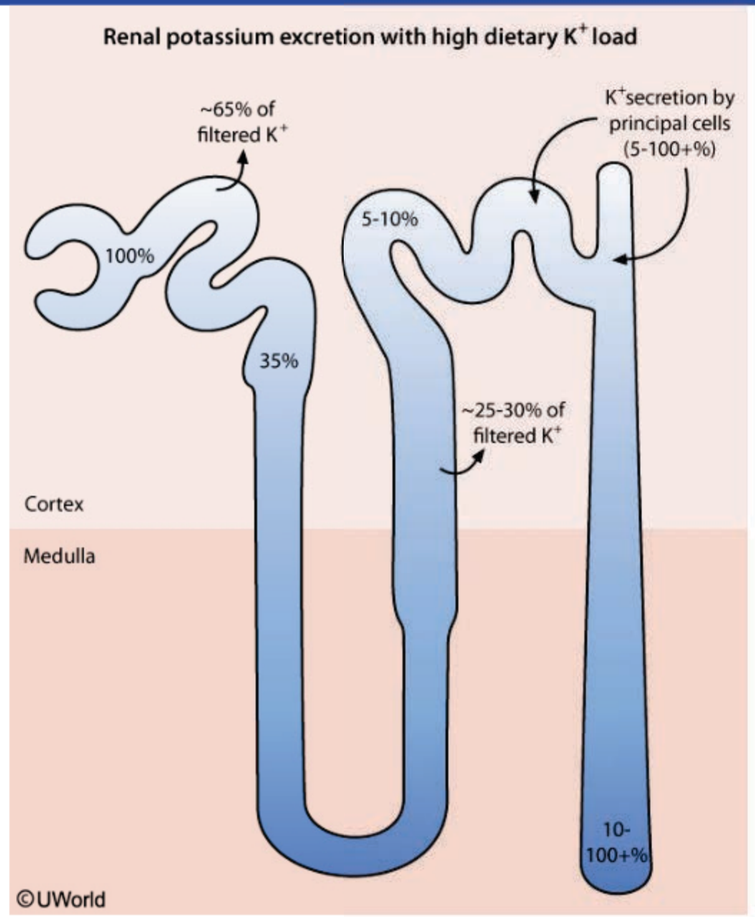
Renal potassium excretion with high dietary K^+ load

~65% of filtered K^+

K^+ secretion by principal cells (5-100+%)

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Several segments of the nephron are involved in the management of potassium (K^+). However, most handle K^+ at a relatively fixed rate that is independent of potassium load and do not play a significant role in the regulation of K^+ excretion in the urine. These segments include the following:

- Bowman's capsule: Because **K^+ is freely filtered** across the glomerular membrane, the amount of K^+ within Bowman's space is equal to that in the glomerular capillaries (ie, 100%) **(Choice C)**.
- The proximal tubule: Approximately 65% of the filtered K^+ load is reabsorbed in the proximal tubule, leaving **~35%** of the total filtered load.
- The thick ascending limb of the loop of Henle: Further resorbs about 25%-30% of the filtered K^+ load through the action of the $Na^+/K^+/2Cl^-$ cotransporter, resulting in only **5-10% of K^+** remaining in the tubular fluid after this segment **(Choices B and D)**.

Because this is a stable process, even in hyperkalemic states, patients will **reabsorb the majority of filtered K^+** in the **proximal tubule** and **loop of Henle.**

Potassium regulation is therefore primarily mediated by the principal and α-intercalated cells of the late distal and cortical collecting tubules. Hypokalemia stimulates reabsorption of K^+ via apically located H^+/K^+-ATPases on α-intercalated cells and can cause the amount of K^+ in the collecting tubule to approach 1% of the filtered load. Conversely, an **increased K^+ load** stimulates principal cells to secrete K^+ through apical K^+ channels. High dietary K^+ intake can cause the amount of K^+ in the **collecting tubules** to actually exceed the filtered load (ie, **>100%**).

Excessive K^+ intake increases K^+ excretion through the following mechanisms:

- High extracellular K^+ levels directly stimulate basolateral Na^+/K^+ pumps on principal cells, increasing K^+ secretion into the tubular fluid.
- Elevated K^+ levels also increase aldosterone secretion, which further enhances activity of principal cell Na^+/K^+ pumps and also increases their apical permeability to Na^+ and K^+ (leading to K^+ loss in the tubular fluid).

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Educational objective:
K^+ is freely filtered by the glomeruli and is mostly reabsorbed in the proximal tubule and loop of Henle. As such,

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- The proximal tubule: Approximately 65% of the filtered K^+ load is reabsorbed in the proximal tubule, leaving **~35%** of the total filtered load.
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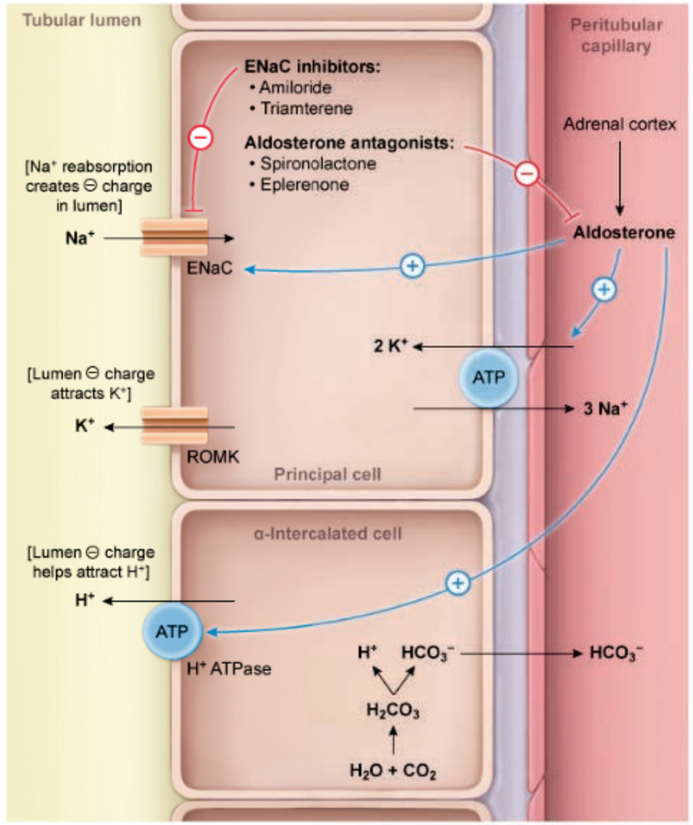
Educational objective:
K^+ is freely filtered by the glomeruli and is mostly reabsorbed in the proximal tubule and loop of Henle. As such, the late distal and cortical collecting tubules are the primary sites for regulation of K^+ excretion in the urine. K^+ depletion stimulates α-intercalated cells to reabsorb extra potassium; principal cells secrete K^+ under conditions of increased K^+ load.

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- The proximal tubule: Approximately 65% of the filtered K^+ load is reabsorbed in the proximal tubule, leaving

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Action of aldosterone in the collecting duct of the nephron



ENaC = epithelial sodium channel; **ROMK** = renal outer medullary potassium channel. ©UWorld

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increased K^+ load.

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A 16-year-old boy is brought to the emergency department with sudden onset of left-sided abdominal pain and blood in his urine. The pain waxes and wanes in intensity and does not improve with rest or position changes. He has a lengthy history of similar pain episodes, but this is the first time he has had gross hematuria. Physical examination shows costovertebral angle tenderness on the left side. Microscopic examination of the urine is shown below.

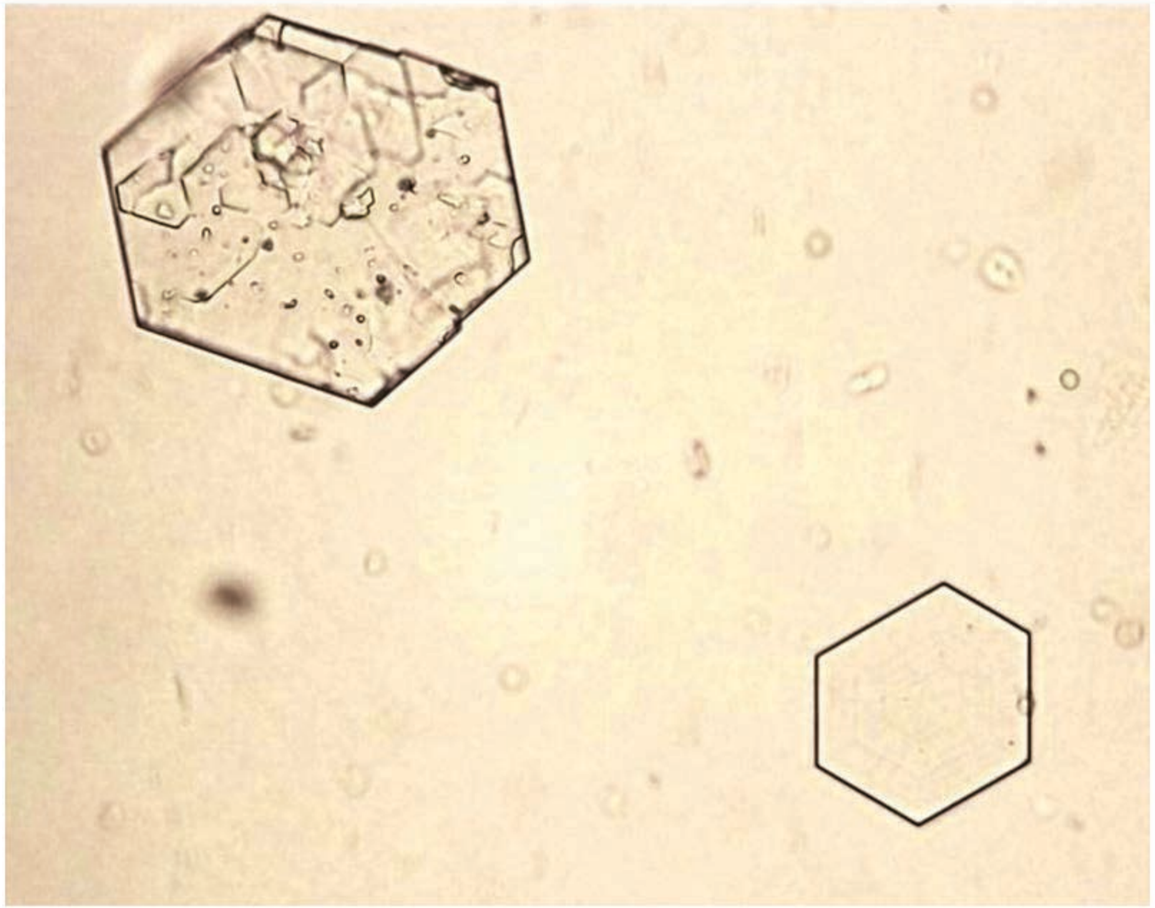


Further laboratory evaluation is most likely to reveal which of the following abnormalities in this patient?

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Further laboratory evaluation is most likely to reveal which of the following abnormalities in this patient?

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Further laboratory evaluation is most likely to reveal which of the following abnormalities in this patient?

- A. Aminoaciduria
- B. Hypercalciuria
- C. Hyperoxaluria
- D. Hyperuricosuria
- E. Hypocitraturia

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Further laboratory evaluation is most likely to reveal which of the following abnormalities in this patient?

- ✓ A. Aminoaciduria (50%)
- ✗ B. Hypercalciuria (9%)
- C. Hyperoxaluria (13%)
- D. Hyperuricosuria (11%)
- E. Hypocitraturia (14%)

Incorrect
Correct answer
A

50%
Answered correctly

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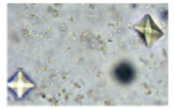
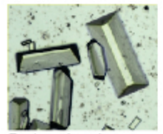
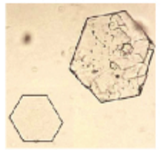
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Explanation

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Nephrolithiasis

Content	Frequency	Radiograph opacity	pH	Microscopic appearance
Calcium oxalate	70%-80%	↑↑	--	 • Octahedron (square with an "X" in the center)
Calcium phosphate			>7.0	• Elongated, wedge-shaped • Forms rosettes
Magnesium ammonium phosphate (struvite or triple phosphate)	15%	↑	>7.0	 • Rectangular prism ("coffin lids")
Uric acid	5%	--	<7.0	 • Yellow or red-brown, diamond or rhombus
Cystine	1%	↑	<7.0	 • Flat, yellow, **hexagonal**

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Recurrent nephrolithiasis in a young patient should raise suspicion for **cystinuria**, which is confirmed by the pathognomonic finding of **hexagonal-shaped crystals** on urinalysis. Cystinuria is an autosomal recessive disorder affecting the high-affinity, sodium-independent dibasic amino acid transporter found on the apical membrane of intestinal and proximal renal tubular epithelial cells. This prevents cystine (cysteine homodimer that forms disulfide bonds) and dibasic amino acids (eg, ornithine, lysine, and arginine) from being reabsorbed in the proximal renal tubules, leading to urine supersaturation with cystine and formation of **cystine stones** (ornithine, lysine, and arginine are relatively soluble in the urine and do not form stones).

Patients with suspected cystinuria without cystine crystals on urinalysis can be diagnosed by detecting elevated urinary cystine levels (ie, **aminoaciduria**). The **sodium cyanide-nitroprusside test** is a qualitative screening test that detects the presence of urinary cystine. Cyanide is initially added to the urine, converting cystine to cysteine. Afterward, nitroprusside is added and reacts with the sulfhydryl group on free cysteine, causing a red-purple discoloration (positive test). Treatment of cystinuria involves increasing hydration and **urinary alkalinization** (eg, acetazolamide).

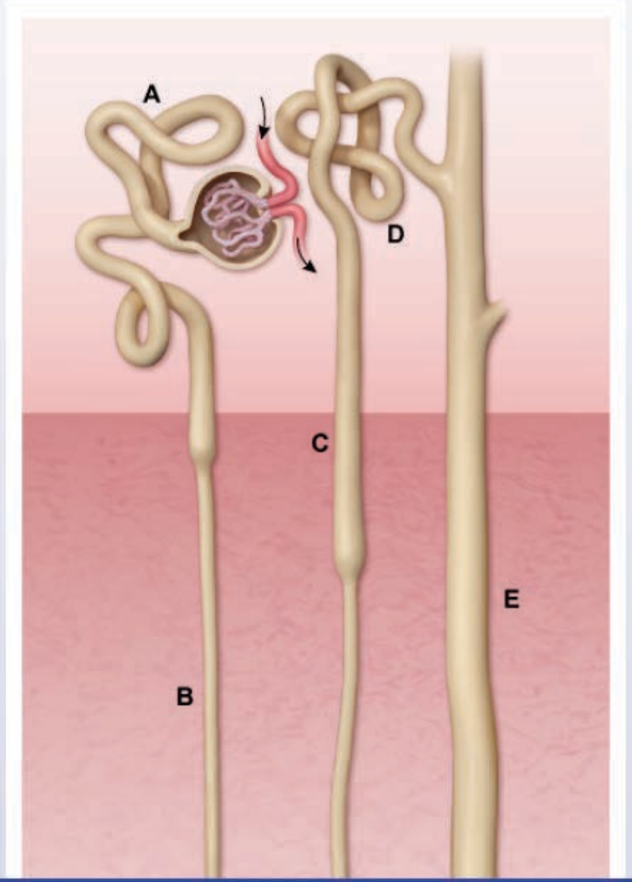
(Choices B, C, D, and E) Hypercalciuria (eg, sarcoidosis), hyperoxaluria (eg, Crohn disease), and hypocitraturia (eg, distal renal tubular acidosis) are risk factors for recurrent calcium stone formation; high concentrations of calcium or oxalate promote precipitation into stones, while citrate inhibits stone formation by complexing with calcium in the urine, preventing spontaneous nucleation and crystal growth. Hyperuricosuria (eg, gout) is a risk factor for recurrent uric acid stones, particularly in the setting of low urine pH.

Educational objective:
Cystinuria results from defective cystine reabsorption by proximal renal tubular epithelial cells. It most often presents with recurrent stone formation at a young age. Urinalysis shows pathognomonic hexagonal cystine crystals, and the sodium cyanide-nitroprusside test can be used to detect excess cystine in the urine.

Pathology	Renal, Urinary Systems & Electrolytes	Cystinuria
Subject	System	Topic

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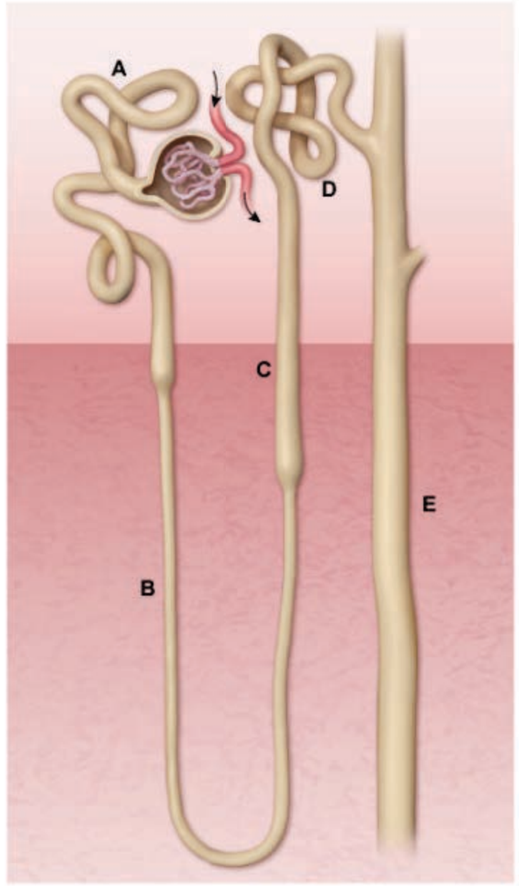
A 62-year-old man comes to the emergency department with severe shortness of breath and orthopnea. His medical history is significant for long-standing hypertension and myocardial infarction a year ago. Physical examination reveals elevated jugular venous pressure, crackles on lung auscultation, and pitting edema of the lower extremities. The patient is given a medication and experiences brisk diuresis with significant symptom relief. The drug most likely used to treat this patient's condition predominantly acts on which of the following nephron segments?



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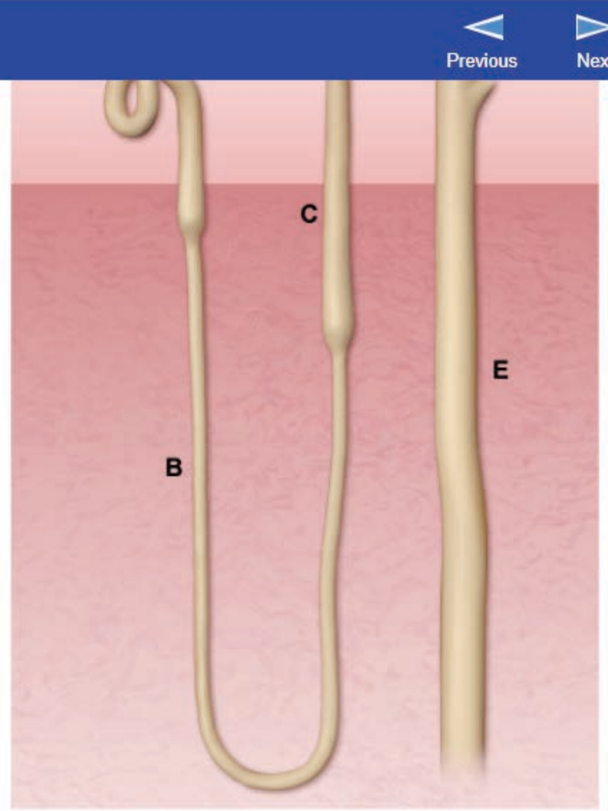
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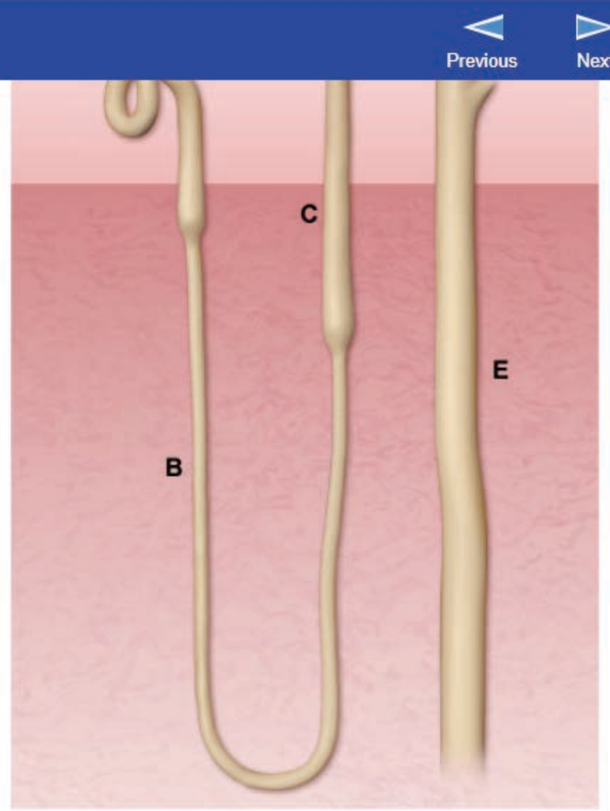
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- A. A
- B. B
- C. C
- D. D
- E. E

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- A. A (3%)
- ✗ B. B (8%)
- ✓ C. C (75%)
- D. D (7%)
- E. E (4%)

Incorrect
Correct answer
C

75%
Answered correctly

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Incorrect
Correct answer

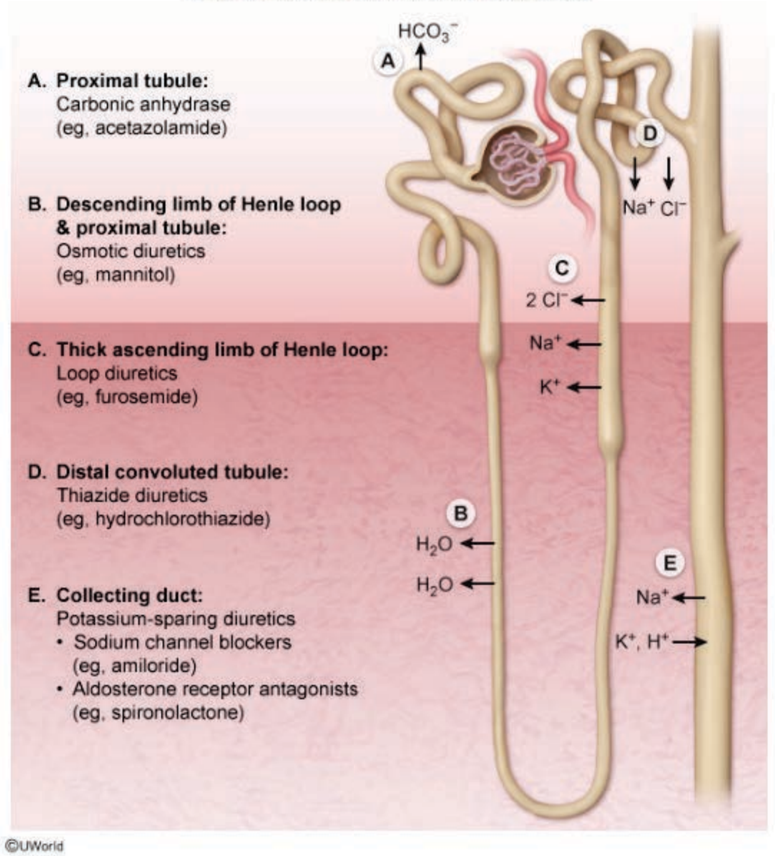
75%
Answered correctly

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Site of action for various diuretics



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This patient with dyspnea and volume overload (ie, elevated jugular venous pressure, edema, lung crackles) has **acute decompensated heart failure**. Patients with heart failure and volume overload are typically treated with **loop diuretics** due to their potent natriuretic effect, which helps reduce vascular congestion and peripheral edema.

Loop diuretics (eg, furosemide, torsemide, bumetanide) inhibit the **Na-K-2Cl symporter** in the apical membranes of cells in the **thick ascending limb of Henle's loop**. Blockade of Na^+ and Cl^- reabsorption from the tubular lumen decreases the medullary concentration gradient, impairing the kidney's ability to concentrate urine and increasing the overall excretion of Na^+, Cl^-, and H_2O. Adverse effects of loop diuretics include electrolyte abnormalities (eg, hypokalemia, hypomagnesemia) and ototoxicity.

(Choice A) Carbonic anhydrase inhibitors (acetazolamide) block the reabsorption of NaCl and $NaHCO_3$ in the proximal tubule. They are weak diuretic agents typically used to treat glaucoma and altitude sickness.

(Choice B) Mannitol is a nonreabsorbable sugar alcohol that functions as an osmotic diuretic by decreasing sodium and water reabsorption by the proximal tubule and descending limb of the loop of Henle. It is used for treating cerebral edema, but causes initial intravascular volume expansion that can worsen pulmonary edema and heart failure.

(Choice D) Thiazide diuretics act by inhibiting NaCl reabsorption in the distal convoluted tubule. Compared to the loop of Henle, this segment reabsorbs only a small proportion of the filtered NaCl load, leading to a smaller natriuretic effect than loop diuretics. Thiazides are mostly used to treat hypertension and are not as effective as loop diuretics for reducing volume overload in heart failure.

(Choice E) The collecting tubules and ducts are the primary site of action of sodium channel blockers (eg, amiloride, triamterene) and aldosterone receptor antagonists (eg, spironolactone, eplerenone). These are weak diuretics that are not effective for diuresis in patients with decompensated heart failure. However, long-term use of aldosterone receptor antagonists improves survival in patients with severe left ventricular systolic dysfunction.

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Loop diuretics (eg, furosemide, torsemide, bumetanide) inhibit the **Na-K-2Cl symporter** in the apical membranes of cells in the **thick ascending limb of Henle's loop**. Blockade of Na^+ and Cl^- reabsorption from the tubular lumen decreases the medullary concentration gradient, impairing the kidney's ability to concentrate urine and increasing the overall excretion of Na^+, Cl^-, and H_2O. Adverse effects of loop diuretics include electrolyte abnormalities (eg, hypokalemia, hypomagnesemia) and ototoxicity.

(Choice A) Carbonic anhydrase inhibitors (acetazolamide) block the reabsorption of NaCl and $NaHCO_3$ in the proximal tubule. They are weak diuretic agents typically used to treat glaucoma and altitude sickness.

(Choice B) Mannitol is a nonreabsorbable sugar alcohol that functions as an osmotic diuretic by decreasing sodium and water reabsorption by the proximal tubule and descending limb of the loop of Henle. It is used for treating cerebral edema, but causes initial intravascular volume expansion that can worsen pulmonary edema and heart failure.

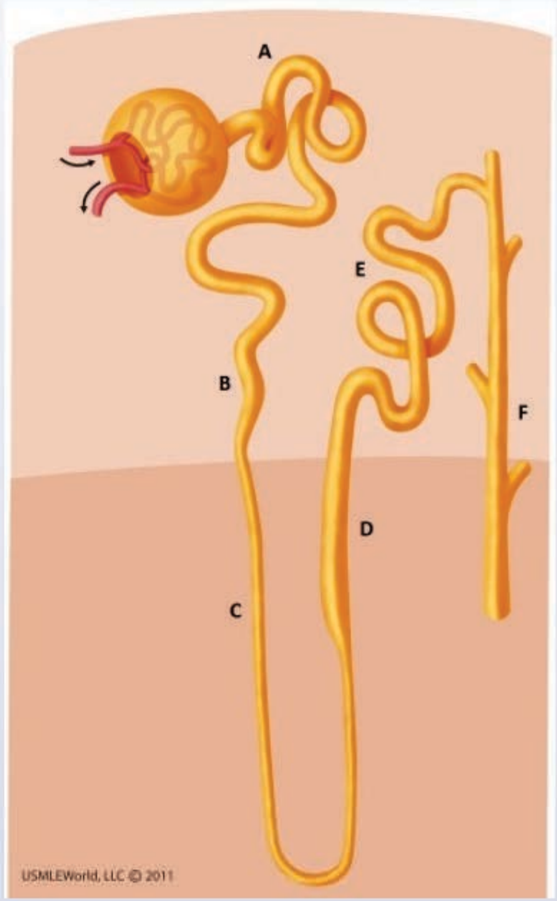
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Educational objective:
Loop diuretics act by inhibiting the Na-K-2Cl cotransporter in the thick ascending limb of the loop of Henle, increasing Na^+, Cl−, and H_2O excretion. They are the most potent diuretics and are used as first-line therapy for rapid relief of symptoms in patients with acute decompensated heart failure.

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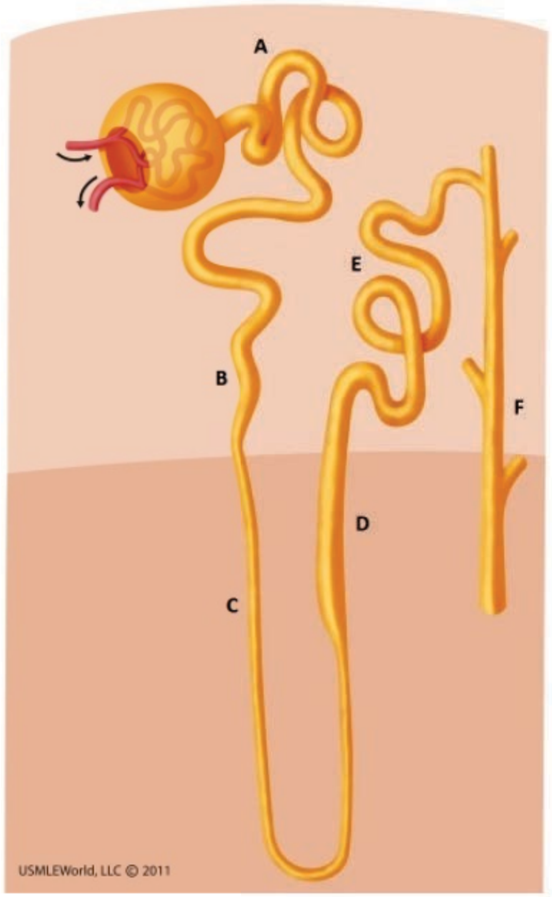
A 62-year-old man comes to the physician for a follow-up appointment. He experienced acute myocardial infarction 2 years ago and has a long history of hypertension. After physical examination and laboratory testing, the physician decides to increase the dose of his diuretic. Repeat laboratory studies indicate that his serum calcium level increases after this adjustment. The diuretic used in this patient acts predominantly on which of the following nephron segments?



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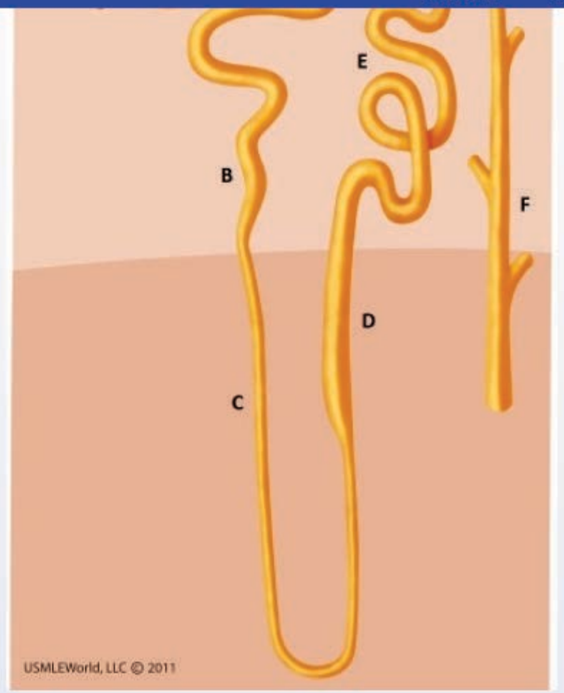
Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

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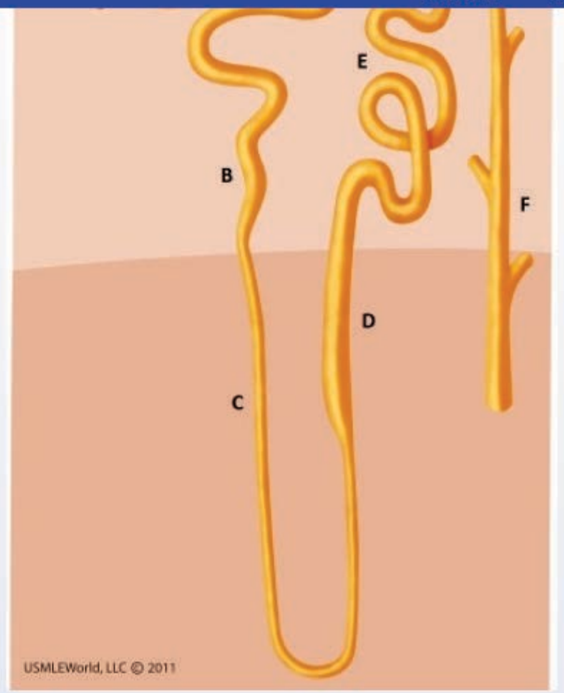
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- A. A
- B. B
- C. C
- D. D
- E. E
- F. F

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- A. A (3%)
- ✕ B. B (1%)
- C. C (1%)
- D. D (8%)
- ✓ E. E (83%)
- F. F (1%)

Incorrect
Correct answer
E

83%
Answered correctly

11 secs
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Major side effects of commonly used diuretics	
Loop diuretics *furosemide, bumetanide, torsemide*	Hypokalemia, hypomagnesemia, hypocalcemia, and ototoxicity
Thiazide diuretics *chlorthalidone, hydrochlorothiazide*	Hypokalemia, hyponatremia, **hyperuricemia**, and **hypercalcemia**
Potassium sparing diuretics *triamterene, spironolactone*	*All:* hyperkalemia *Spironolactone:* gynecomastia, antiandrogen effects
Carbonic anhydrase inhibitors *acetazolamide*	Metabolic acidosis
Osmotic diuretics *mannitol*	Hypernatremia, pulmonary edema

Thiazide diuretics work in the distal convoluted tubule, causing enhanced Na^+, Cl^-, and water excretion. The apical membrane of early distal tubule cells contains the Na^+/Cl^- symporter while the basolateral side has Na^+/K^+ ATPases and Cl^- channels that maintain a NaCl gradient across the apical cell membrane. Thiazides inhibit the apical Na^+/Cl^- symporter, decreasing luminal NaCl absorption into the distal tubular cell. This can cause hypercalcemia by reducing intracellular Na^+ concentrations, which in turn increases the activity of the basolateral Na^+-Ca^{2+} exchanger. The resulting reduction in intracellular Ca^{2+} levels acts to increase luminal Ca^{2+} absorption in the distal tubule. Increased Ca^{2+} absorption in the proximal tubule secondary to volume depletion can also

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There are a number of thiazide and thiazide-like diuretics available. Examples include hydrochlorothiazide, chlorothiazide, indapamide, and metolazone. They differ in potency, bioavailability, and half-life. Thiazides are not as efficacious as loop diuretics as only a small amount of filtered Na reaches the distal tubules. They are used to treat edema secondary to heart failure, renal disease, and liver disease. Thiazides are also commonly used to treat hypertension. More common side effects include hypokalemia, hyponatremia, and hypomagnesemia. Less common side effects include hypotension, volume depletion, and hypercalcemia.

(Choices A and B) Carbonic anhydrase inhibitors block the reabsorption of $NaHCO_3$ and work in the convoluted and straight portions of the proximal tubule.

(Choice C) Osmotic diuretics such as mannitol function mainly in the proximal tubule and the descending limb of the loop of Henle to reduce Na and water reabsorption.

(Choice D) Loop diuretics work in the thick ascending limb and are the most potent diuretics.

(Choice F) The collecting duct system includes the connecting tubules and ducts. Here, aldosterone and ADH make final adjustments to electrolytes and water content. Potassium- sparing diuretics and aldosterone antagonists work in the collecting duct.

Educational objective:

Thiazide diuretics work by blocking Na^+-Cl^- symporters in the distal convoluted tubules, causing enhanced Na, Cl

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apical Na^+/Cl^- symporter, decreasing luminal NaCl absorption into the distal tubular cell. This can cause hypercalcemia by reducing intracellular Na^+ concentrations, which in turn increases the activity of the basolateral Na^+-Ca^{2+} exchanger. The resulting reduction in intracellular Ca^{2+} levels acts to increase luminal Ca^{2+} absorption in the distal tubule. Increased Ca^{2+} absorption in the proximal tubule secondary to volume depletion can also contribute to hypercalcemia in thiazide-treated patients.

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Educational objective:
Thiazide diuretics work by blocking Na^+-Cl^- symporters in the distal convoluted tubules, causing enhanced Na, Cl, and water excretion. Since only a small amount of filtered Na^+ reaches the distal tubules, thiazides are not as efficacious as loop diuretics. Unlike loop diuretics, thiazides can cause hypercalcemia.

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A 52-year-old woman comes to the office due to episodic incontinence for the last several months. She states that these episodes occur almost every day and are very embarrassing. They begin as an urge to urinate, and most of the time she cannot make it to the bathroom before urinating on herself. Physical examination, including pelvic examination, is unremarkable. A urinalysis is within normal limits. Urodynamic evaluation is significant for detrusor instability. Initial non-pharmacologic measures are unsuccessful and pharmacologic therapy is considered. The appropriate treatment for this patient's condition includes an agent with which of the following effects?

- A. Antagonism of alpha-1 adrenoreceptors
- B. Antagonism of beta-1 adrenoreceptors
- C. Antagonism of muscarinic cholinergic receptors
- D. Antagonism of nicotinic cholinergic receptors
- E. Stimulation of alpha-2 adrenoreceptors
- F. Stimulation of beta-2 adrenoreceptors

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- A. Antagonism of alpha-1 adrenoreceptors (8%)
- ✗ B. Antagonism of beta-1 adrenoreceptors (1%)
- ✓ C. Antagonism of muscarinic cholinergic receptors (79%)
- D. Antagonism of nicotinic cholinergic receptors (3%)
- E. Stimulation of alpha-2 adrenoreceptors (3%)
- F. Stimulation of beta-2 adrenoreceptors (2%)

Incorrect
Correct answer
C

79%
Answered correctly

03 secs
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Explanation

Characteristics of muscarinic acetylcholine receptors			
Receptor	Target organ(s)	Effect of stimulation	Effect of inhibition

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Characteristics of muscarinic acetylcholine receptors			
Receptor	**Target organ(s)**	**Effect of stimulation**	**Effect of inhibition**
M_1	Brain	Memory formation/cognitive functioning	Confusion
M_2	Heart	Decreased heart rate & atrial contraction	Increased heart rate & contractility
M_3	Peripheral vasculature	Smooth muscle relaxation, vasodilation, hypotension	Smooth muscle contraction, vasoconstriction, hypertension
	Lungs	Bronchoconstriction	Bronchodilation
	Bladder	Detrusor contraction	Detrusor relaxation, urinary retention
	Eyes	Pupillary sphincter muscle contraction (miosis), ciliary muscle contraction (accommodation)	Mydriasis, cycloplegia, may precipitate acute angle glaucoma in elderly patients
	Gastrointestinal tract	Increased peristalsis, increased salivary &	Constipation, dry mouth, decreased

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	Brain	formation/cognitive functioning	Sedation
M_2	Heart	Decreased heart rate & atrial contraction	Increased heart rate & contractility
M_3	Peripheral vasculature	Smooth muscle relaxation, vasodilation, hypotension	Smooth muscle contraction, vasoconstriction, hypertension
	Lungs	Bronchoconstriction	Bronchodilation
	Bladder	Detrusor contraction	Detrusor relaxation, urinary retention
	Eyes	Pupillary sphincter muscle contraction (miosis), ciliary muscle contraction (accommodation)	Mydriasis, cycloplegia, may precipitate acute angle glaucoma in elderly patients
	Gastrointestinal tract	Increased peristalsis, increased salivary & gastric secretions	Constipation, dry mouth, decreased acid production
	Skin	Increased sweat production	Increased temperature (from decreased sweating)

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			sweating)

This patient has **urge incontinence**, or overactive bladder syndrome, which is caused by uninhibited bladder contractions (detrusor instability). This causes a sudden sensation of urgency, with involuntary leakage of urine often occurring before reaching the toilet.

Pharmacologic therapy with **anticholinergic drugs** is useful for treating the condition. These agents (eg, oxybutynin) antagonize muscarinic receptors, primarily the **M_3 receptors** present on smooth muscle cells in the bladder. Antagonism of M_3 receptors decreases the production of IP_3 and the release of calcium, leading to smooth muscle relaxation. This causes **decreased involuntary detrusor contractions**, increased bladder capacity, and decreased sense of urgency.

Antimuscarinic agents often act on several types of muscarinic receptors and should be used with caution, especially in elderly patients. These agents should be started at the lowest possible dose and titrated as needed to minimize anticholinergic side effects (dry mouth, blurred vision, tachycardia, drowsiness, and constipation).

(Choice A) Alpha1-blockers such as doxazosin, prazosin and terazosin are useful for the treatment of both benign prostatic hyperplasia (BPH) and hypertension. They cause relaxation of the smooth muscle in arterial and venous walls, leading to a decrease in peripheral vascular resistance. In patients with BPH, they also induce relaxation of the smooth muscle in the bladder neck and prostate, leading to a decrease in urinary obstruction.

(Choice B) Beta-1 receptors are found in cardiac tissue and on renal juxtaglomerular cells. Selective beta-1 blockers (eg, metoprolol) decrease heart rate and contractility, and block catecholamine-induced renin release by the kidney.

(Choice D) Nicotinic cholinergic receptors are found on postganglionic neurons in sympathetic and parasympathetic ganglia and on skeletal muscle cells at the neuromuscular junction. Drugs that block skeletal muscle nicotinic receptors, such as tubocurarine, are often used during general anesthesia to induce paralysis.

(Choice E) Central sympatholytics such as methyldopa and clonidine stimulate alpha-2 receptors centrally, which causes a decrease in generalized sympathetic outflow and a decrease in blood pressure. Rebound hypertension

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to minimize anticholinergic side effects (dry mouth, blurred vision, tachycardia, drowsiness, and constipation).

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(Choice E) Central sympatholytics such as methyldopa and clonidine stimulate alpha-2 receptors centrally, which causes a decrease in generalized sympathetic outflow and a decrease in blood pressure. Rebound hypertension is a concern with abrupt cessation.

(Choice F) Beta-2 adrenergic receptors are located in the smooth muscle of airways, peripheral vasculature, and uterus. Stimulation of these receptors causes bronchodilation, vasodilation, and tocolysis, respectively. In contrast, bladder relaxation is mediated primarily by beta-3 adrenergic receptors.

Educational objective:
Urge incontinence, or overactive bladder syndrome, is caused by uninhibited bladder contractions (detrusor instability). It results in a sense of urgency accompanied by an involuntary loss of urine. If behavioral therapy alone is unsuccessful, pharmacologic therapy with an antimuscarinic drug (targeting M_3 receptors) can help improve symptoms.

References

- Antimuscarinic agents: implications and concerns in the management of overactive bladder in the elderly

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A 30-year-old woman has had diarrhea and weight loss for the past several months. She also has diffuse bone pain and generalized weakness. The patient has a history of primary hypothyroidism for which she takes levothyroxine. She is 162.5 cm (5 ft 4 in) tall and weighs 45 kg (99.2 lb). BMI is 17 kg/m^2. On physical examination, the abdomen is soft and nontender. Initial laboratory evaluation reveals microcytic anemia, hypoalbuminemia, normal magnesium level, and normal serum TSH concentration. The patient is found to have positive anti-tissue transglutaminase IgA antibodies. Which of the following sets of additional laboratory findings are most likely present in this patient?

	Serum calcium	Serum phosphorus	Serum parathyroid hormone
○ A.	↑	↓	↑
○ B.	↓	↓	↑
○ C.	↓	↑	↓
○ D.	↓	↑	↑
○ E.	normal	↑	↑

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	Serum calcium	Serum phosphorus	Serum parathyroid hormone	
✗ A.	↑	↓	↑	(25%)
✓ B.	↓	↓	↑	(41%)
C.	↓	↑	↓	(11%)
D.	↓	↑	↑	(18%)
E.	normal	↑	↑	(3%)

Incorrect
Correct answer
B

41%
Answered correctly

04 secs
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Explanation

This patient with diarrhea, weight loss, and a positive tissue transglutaminase antibody assay has celiac disease,

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This patient with diarrhea, weight loss, and a positive tissue transglutaminase antibody assay has celiac disease, an immune-mediated hypersensitivity to dietary gluten. **Celiac disease** is characterized by villous atrophy in the small intestine, leading to **malabsorption** of dietary fats and fat-soluble vitamins (ie, A, D, E, K). The resulting **vitamin D deficiency** can present as rickets in children and osteomalacia in adults.

Vitamin D increases intestinal absorption of calcium and phosphorus; deficiency reduces calcium absorption, which in turn stimulates release of parathyroid hormone (PTH). Vitamin D also directly inhibits PTH release, and therefore vitamin D deficiency facilitates a significant rise in PTH (secondary hyperparathyroidism). PTH induces release of calcium and phosphorus from bones, leading to decreased bone mineralization. (Although most phosphorus in the body is in the form of hydroxyapatite in bone, circulating phosphorus is primarily in the form of phosphate/phosphoric acids.)

Typical laboratory findings in vitamin D deficiency include:

- **low 25-hydroxyvitamin D**, which reflects total body vitamin D stores (PTH stimulates renal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D; therefore, 1,25-dihydroxyvitamin D may remain within laboratory norms).
- **elevated PTH**.
- increased alkaline phosphatase, reflecting increased bone turnover.
- **low serum phosphorus**, due to decreased intestinal absorption and increased PTH-mediated renal excretion.

PTH may initially maintain normal serum calcium levels by reducing urinary calcium excretion. However, hypocalcemia may eventually develop as bone stores are depleted in later or more severe cases.

(Choice A) Primary hyperparathyroidism presents with elevated PTH, mild hypercalcemia, and low serum phosphorus (due to increased renal excretion) but is usually due to a parathyroid adenoma and is not associated

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- **elevated PTH**.
- increased alkaline phosphatase, reflecting increased bone turnover.
- **low serum phosphorus**, due to decreased intestinal absorption and increased PTH-mediated renal excretion.

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(Choice A) Primary hyperparathyroidism presents with elevated PTH, mild hypercalcemia, and low serum phosphorus (due to increased renal excretion) but is usually due to a parathyroid adenoma and is not associated with celiac disease.

(Choice C) In hypoparathyroidism, low serum PTH is accompanied by hypocalcemia and an increase in serum phosphorus. Hypoparathyroidism can be caused by severe hypomagnesemia, which can be seen with prolonged diarrhea, but this patient's magnesium level is normal.

(Choices D and E) Chronic kidney disease causes hyperphosphatemia due to decreased filtration and excretion of phosphate. Concurrently, there is decreased renal production of 1,25-dihydroxyvitamin D (the activated form) due to inadequate renal metabolic activity and suppression of 1-alpha-hydroxylase by hyperphosphatemia. Hypocalcemia may be present, although increased PTH sometimes maintains calcium within laboratory norms. Pseudohypoparathyroidism is characterized by resistance to PTH and presents with similar biochemical markers.

Educational objective:
Malabsorption caused by celiac disease can lead to vitamin D deficiency. Patients have decreased serum phosphorus, increased serum parathyroid hormone (secondary hyperparathyroidism), and low (or normal) serum calcium.

References

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A 78-year-old woman is brought to the office by her son for follow-up. The patient was hospitalized 5 days ago due to fever, vomiting, dysuria, and flank pain. Acute pyelonephritis was diagnosed, and she was treated with ceftriaxone and given intravenous fluids. Urine culture grew *Escherichia coli*, and the patient was discharged home with a prescription for levofloxacin, which she is still taking. Since hospital discharge, the patient has had nausea and loss of appetite, but her fever and urinary symptoms have resolved. Temperature is 36.4 C (97.5 F), blood pressure is 116/68 mm Hg, and pulse is 92/min. No suprapubic or flank tenderness is noted on physical examination. Laboratory results are as follows:

Serum chemistry	
Sodium	144 mEq/L
Potassium	3.6 mEq/L
Blood urea nitrogen	44 mg/dL
Creatinine	1.7 mg/dL
Urinalysis	
Protein	none
Blood	negative
Cells	none
Casts	none
Urine sodium	10 mEq/L (normal: ≥20)

Renal function was normal at the time of hospital discharge. A review of hospital records shows no significant hypotensive episodes or radiographic contrast exposure during the hospital stay. Which of the following is the

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Blood urea nitrogen	44 mg/dL
Creatinine	1.7 mg/dL
Urinalysis	
Protein	none
Blood	negative
Cells	none
Casts	none
Urine sodium	10 mEq/L (normal: ≥20)

Renal function was normal at the time of hospital discharge. A review of hospital records shows no significant hypotensive episodes or radiographic contrast exposure during the hospital stay. Which of the following is the most likely cause of this patient's renal dysfunction?

- A. Chronic pyelonephritis
- B. Interstitial nephritis
- C. Prerenal azotemia
- D. Renal artery stenosis
- E. Tubular necrosis
- F. Urinary tract obstruction

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Blood urea nitrogen	44 mg/dL
Creatinine	1.7 mg/dL
Urinalysis	
Protein	none
Blood	negative
Cells	none
Casts	none
Urine sodium	10 mEq/L (normal: ≥20)

Renal function was normal at the time of hospital discharge. A review of hospital records shows no significant hypotensive episodes or radiographic contrast exposure during the hospital stay. Which of the following is the most likely cause of this patient's renal dysfunction?

- A. Chronic pyelonephritis (3%)
- ✗ B. Interstitial nephritis (23%)
- ✓ C. Prerenal azotemia (50%)
- D. Renal artery stenosis (3%)
- E. Tubular necrosis (13%)
- F. Urinary tract obstruction (5%)

Incorrect
Correct answer
C

50%
Answered correctly

05 secs
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Explanation

Prerenal acute kidney injury	
Etiology	• Decreased renal perfusion ◦ True volume depletion ◦ Decreased EABV (eg, heart failure, cirrhosis) ◦ Displacement of intravascular fluid (eg, sepsis, pancreatitis) ◦ Bilateral renal artery stenosis with ACE inhibition ◦ Afferent arteriole vasoconstriction (eg, NSAIDs)
Clinical features	• Increase in serum creatinine (eg, 50% from baseline) • Decreased urine output • Blood urea nitrogen/creatinine ratio >20:1 • Fractional excretion of sodium <1% • Unremarkable (bland) urine sediment
Treatment	• Restoration of renal perfusion
EABV = effective arterial blood volume; **NSAID** = nonsteroidal anti-inflammatory drug.	

This patient developed **reduced renal function** (ie, elevated creatinine) following hospitalization for acute pyelonephritis. Her appetite loss (which often persists during recovery from illness and can be worsened by antibiotic use) likely resulted in **decreased oral intake** with subsequent hypovolemia and decreased renal perfusion.

Impaired renal function due to hypoperfusion is termed **prerenal** acute kidney injury (**AKI**), as the pathogenesis is driven by impaired renal blood flow; the kidneys are not actually injured and renal tubular function is intact. In response to perceived hypovolemia, the renin-angiotensin-aldosterone system (RAAS) becomes activated, and

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- **Increased ratio** of blood urea nitrogen (BUN) to creatinine (>20:1) (ie, **prerenal azotemia**) due to increased urea reabsorption
- **Low urine sodium** (<20 mEq/L) and low (<1%) fractional excretion of sodium (FENa) due to increased sodium reabsorption
- High urine osmolality (>450 mOsm/kg) and specific gravity (>1.015), in part due to nonosmotic stimulation of antidiuretic hormone (ADH) with relatively greater reabsorption of water than solute
- **Unremarkable urinalysis** (eg, no protein, cells, or casts) due to lack of intrinsic kidney injury

Restoration of intravascular volume (eg, isotonic intravenous fluids) normalizes RAAS and ADH activity and resolves prerenal AKI.

(Choice A) Chronic pyelonephritis can be a complication of repeated or untreated episodes of acute pyelonephritis. However, urinalysis typically shows white blood cells (WBCs) and other evidence of kidney injury (eg, hematuria, proteinuria).

(Choice B) Acute interstitial nephritis can occur following new medication exposure (eg, levofloxacin). However, urinary WBCs and WBC casts are usually present, and laboratory findings are consistent with intrinsic kidney injury

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antidiuretic hormone (ADH) with relatively greater reabsorption of water than solute

- **Unremarkable urinalysis** (eg, no protein, cells, or casts) due to lack of intrinsic kidney injury

Restoration of intravascular volume (eg, isotonic intravenous fluids) normalizes RAAS and ADH activity and resolves prerenal AKI.

(Choice A) Chronic pyelonephritis can be a complication of repeated or untreated episodes of acute pyelonephritis. However, urinalysis typically shows white blood cells (WBCs) and other evidence of kidney injury (eg, hematuria, proteinuria).

(Choice B) Acute interstitial nephritis can occur following new medication exposure (eg, levofloxacin). However, urinary WBCs and WBC casts are usually present, and laboratory findings are consistent with intrinsic kidney injury (eg, BUN/creatinine ratio ~10:1, FENa >2%).

(Choice D) Renal artery stenosis is typically accompanied by underlying hypertension caused by chronic RAAS activation. Patients are at risk for developing AKI after initiation of an ACE inhibitor.

(Choice E) Untreated prerenal AKI can eventually lead to ischemic acute tubular necrosis. However, muddy brown casts are commonly present, and laboratory findings are more consistent with intrinsic (rather than prerenal) kidney injury.

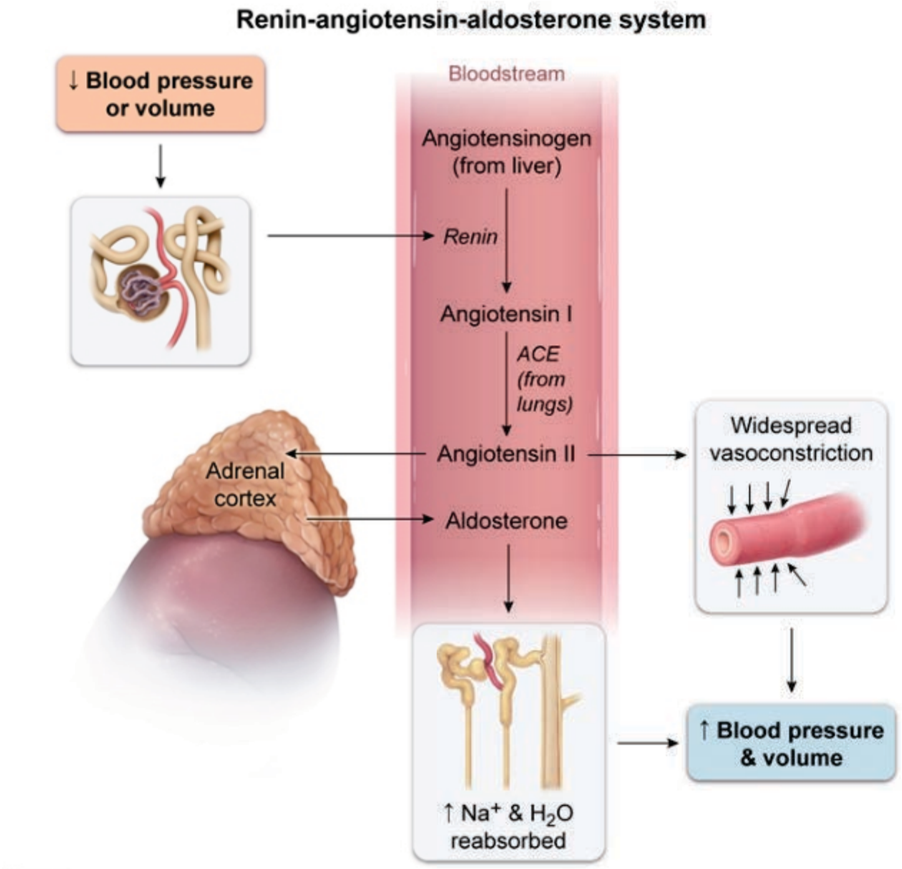
(Choice F) Although common in older men due to urethral obstruction by an enlarged prostate, AKI due to urinary tract obstruction is relatively uncommon in women because it requires obstruction of both ureters (eg, advanced cervical cancer). In addition, postrenal AKI usually demonstrates a BUN/creatinine ratio <20:1.

Educational objective:
Prerenal acute kidney injury results from renal hypoperfusion (eg, dehydration due to poor oral intake). Characteristic laboratory findings include an elevated blood urea nitrogen/creatinine ratio (>20:1), low urine sodium (<20 mEq/L), low fractional excretion of sodium (<1%), high urine osmolality and specific gravity, and unremarkable urinalysis.

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- Fractional excretion of sodium <1%

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Rest
resolves prerenal AKI.

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- Fractional excretion of sodium <1%

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Stimuli for secretion of antidiuretic hormone	
Osmotic	• Serum osmolality > ~285 mOsm/kg H_2O
Nonosmotic	• Nausea • Pain • Physical or emotional stress • Hypotension • Hypovolemia • Hypoxia • Hypoglycemia

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Res
resolves prerenal AKI.

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A study is conducted to standardize laboratory equipment in a hospital network. In one hospital, 2 healthy volunteers undergo testing. Both are found to have a serum creatinine level of 1.1 mg/dL. Glomerular filtration rate is estimated using the same equation and reveals values of 118 mL/min in one volunteer and 70 mL/min in the other. A difference in which of the following parameters best explains the observed laboratory findings in these volunteers?

- A. Basal metabolic rate
- B. Dietary purine intake
- C. Hepatic synthetic function
- D. Renal tubular reabsorption capacity
- E. Skeletal muscle mass

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- A. Basal metabolic rate (11%)
- ✗ B. Dietary purine intake (4%)
- C. Hepatic synthetic function (4%)
- D. Renal tubular reabsorption capacity (25%)
- ✓ E. Skeletal muscle mass (54%)

Incorrect
Correct answer
E

54%
Answered correctly

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Explanation

Creatinine is a waste product generated by the breakdown of creatine in the muscles. It is released from muscle at a relatively constant rate, is neither metabolized nor reabsorbed by the kidneys, and is easily measured; therefore, it can be used to **estimate the glomerular filtration rate** (GFR).

However, creatinine has several **limitations** in the estimation of GFR. Because its formation is due largely to muscle metabolism, **differences in skeletal muscle mass** (eg, higher in body builders and lower in elderly patients, those with amputations) **affect the amount of creatinine synthesized**. Alterations in **dietary intake** can

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However, creatinine has several **limitations** in the estimation of GFR. Because its formation is due largely to muscle metabolism, **differences in skeletal muscle mass** (eg, higher in body builders and lower in elderly patients, those with amputations) **affect the amount of creatinine synthesized**. Alterations in **dietary intake** can also raise (eg, creatine supplements, high-meat diet) or lower (eg, low-protein vegetarian diet) creatinine levels. Therefore, patients with lower muscle mass or reduced dietary meat intake may have significantly lower GFRs for any given creatinine level.

Another potential source of error is the active secretion of creatinine by the proximal tubules; if uncorrected, this results in a slight overestimation of GFR (~10%-20%).

(Choice A) Alterations in basal metabolic rate can explain why individuals can have the same caloric intake but different body weight. However, they do not affect creatinine levels, which is dependent on muscle mass and dietary meat intake.

(Choice B) Increased levels of dietary purines can result in gout formation in predisposed individuals but are not associated with altered creatinine formation.

(Choice C) Creatine (creatinine precursor) is a nonessential nutrient synthesized in the liver and kidney and also obtained from meat consumption; although a disruption in hepatic synthetic function could reduce endogenous creatine production by the liver, continued production by the kidney along with creatine obtained from the diet make hepatic dysfunction alone an unlikely source of altered creatine/creatinine levels.

(Choice D) Creatinine is freely filtered and neither metabolized nor reabsorbed by the kidneys; therefore, tubular reabsorptive function would not affect the GFR.

Educational objective:

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(Choice D) Creatinine is freely filtered and neither metabolized nor reabsorbed by the kidneys; therefore, tubular reabsorptive function would not affect the GFR.

Educational objective:
Creatinine, a waste product generated by the breakdown of creatine in the muscles, is used to estimate the glomerular filtration rate (GFR). Creatinine formation is dependent on muscle mass and meat intake; therefore, patients with low muscle mass (eg, elderly patient, those with amputations) or low intake (eg, low-protein vegetarian diet) can have significantly lower GFRs for any given creatinine level.

Physiology Renal, Urinary Systems & Electrolytes Chronic kidney disease

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A 30-year-old man is admitted to the hospital due to seizures. The repeated, prolonged tonic-clonic seizures were terminated with intravenous lorazepam in the emergency department. Medical history is significant for amphetamine abuse. The patient develops decreased urine output 24 hours after hospital admission. Temperature is 37.1 C (98.8 F), blood pressure is 140/90 mm Hg, pulse is 88/min, and respirations are 18/min. Examination shows bibasilar lung crackles and mild edema of the lower extremities. Laboratory results are as follows:

Serum chemistry	
Blood urea nitrogen	40 mg/dL
Creatinine	4.2 mg/dL
Potassium	6.4 mEq/L
Urinalysis	
Protein	2+
Blood	3+
White blood cells	negative
Red blood cells	negative

Which of the following is the most likely cause of this patient's kidney injury?

- A. Glomerular injury due to immune complexes
- B. Inflammatory reaction of the tubular interstitium
- C. Renal infarction due to arterial obstruction

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- A. Glomerular injury due to immune complexes
- B. Inflammatory reaction of the tubular interstitium
- C. Renal infarction due to arterial obstruction
- D. Tubular injury due to light-chain deposition
- E. Tubular injury due to released hemoglobin
- F. Tubular injury due to released myoglobin

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Serum chemistry

Blood urea nitrogen	40 mg/dL
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Urinalysis

Protein	2+
Blood	3+
White blood cells	negative
Red blood cells	negative

Which of the following is the most likely cause of this patient's kidney injury?

- A. Glomerular injury due to immune complexes (7%)
- ✗ B. Inflammatory reaction of the tubular interstitium (20%)
- C. Renal infarction due to arterial obstruction (10%)
- D. Tubular injury due to light-chain deposition (2%)
- E. Tubular injury due to released hemoglobin (4%)
- ✓ F. Tubular injury due to released myoglobin (54%)

Incorrect
Correct answer
F

54%
Answered correctly

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Rhabdomyolysis	
Risk factors	• Crush injury • Prolonged muscle activity (eg, seizure, marathon running) • Drug/medication use (eg, statins, amphetamines, heroin)
Etiology	• Myocyte necrosis, release of intracellular contents (eg, myoglobin) • Kidney injury: Heme pigment–induced acute tubular necrosis
Laboratory findings	• ↑↑ Creatine kinase • Myoglobinuria (UA with positive blood but no RBCs on microscopy) • Acute kidney injury & electrolyte abnormalities (eg, ↑ K, ↑ P, ↓ Ca)
Ca = calcium; **K** = potassium; **P** = phosphorus; **RBCs** = red blood cells; **UA** = urinalysis.	

This patient with acute kidney injury, hyperkalemia, and urinalysis with 3+ blood but no red blood cells has **rhabdomyolysis**, likely induced by his prolonged seizure. Rhabdomyolysis is characterized by myocyte injury with the release of intracellular muscle contents (ie, myoglobin, electrolytes) into the circulation. It is common in crush injuries, prolonged muscle activity (eg, seizure), or drug use. **Positive blood** on urine dipstick (a reaction that detects the heme pigment in both hemoglobin and myoglobin) in the **absence of red blood cells** on microscopic urinalysis suggests **myoglobinuria**.

Renal injury in rhabdomyolysis results from **myoglobin** filtration and degradation within the glomeruli. **Heme pigment** is released, which causes **acute tubular necrosis** by direct cytotoxicity and renal vasoconstriction. Hyperkalemia, hyperphosphatemia, and hyperuricemia also occur due to myocyte lysis.

(Choice A) Immune complex–mediated glomerular injury is seen in a variety of diseases (eg, IgA nephropathy, poststreptococcal glomerulonephritis), but these diseases do not cause myoglobinuria. Urinary cast formation or severe proteinuria are more common manifestations.

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(Choice B) Acute interstitial nephritis, an inflammatory reaction of the tubular interstitium, is typically associated with a medication exposure (eg, antibiotics) and presents with some combination of fever, eosinophilia, and rash. Urinalysis shows white blood cell casts, not myoglobinuria.

(Choice C) Renal infarctions can be due to thromboembolic or atheroembolic disease and typically occur in older patients with established atherosclerosis or hypercoagulability. Hematuria with red cells would be expected on urinalysis.

(Choice D) Multiple myeloma causes renal injury due to light chain–complex deposition in the renal tubules. This malignancy occurs in older patients and presents with hypercalcemia, anemia, and bone pain. It causes proteinuria (ie, Bence Jones protein), not myoglobinuria.

(Choice E) Tubular injury due to released hemoglobin can also cause a heme pigment–induced kidney injury and may occur with hemolytic diseases (eg, paroxysmal nocturnal hemoglobinuria) or incompatible blood transfusion.

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(Choice E) Tubular injury due to released hemoglobin can also cause a heme pigment–induced kidney injury and may occur with hemolytic diseases (eg, paroxysmal nocturnal hemoglobinuria) or incompatible blood transfusion. However, renal failure after a prolonged seizure is more suggestive of rhabdomyolysis.

Educational objective:
Rhabdomyolysis is characterized by the release of intracellular muscle contents (eg, myoglobin, electrolytes) due to myocyte injury; it is common with crush injuries, seizures, or drug use (eg, statins). Heme pigment (released from myoglobin after degradation in the kidney) is toxic to tubular cells and can cause acute tubular necrosis. Positive blood on urine dipstick in the absence of red blood cells on microscopic urinalysis suggests myoglobinuria.

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A 58-year-old woman comes to the emergency department due to cramping mid-abdominal pain. Imaging shows a small bowel obstruction. Vital signs and laboratory studies, including complete blood count and comprehensive metabolic panel, are within normal limits. The patient is admitted to the hospital for nonsurgical management. Oral intake is withheld to promote bowel rest, and an isotonic saline infusion is administered for hydration. She has no vomiting or diarrhea and after 2 days the abdominal pain improves. Total administration of sodium chloride infusion was approximately 6 L. Which of the following changes have most likely occurred in this patient since the onset of her hospitalization?

	Blood pH	Serum bicarbonate	Serum chloride	Urine sodium
A.	Decreased	Decreased	Decreased	Decreased
B.	Decreased	Decreased	Increased	Increased
C.	Decreased	Increased	Decreased	No change
D.	Increased	Increased	Decreased	Decreased
E.	Increased	Increased	Decreased	Increased

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	Blood pH	Serum bicarbonate	Serum chloride	Urine sodium	
✗ A.	Decreased	Decreased	Decreased	Decreased	(5%)
✓ B.	Decreased	Decreased	Increased	Increased	(55%)
C.	Decreased	Increased	Decreased	No change	(12%)
D.	Increased	Increased	Decreased	Decreased	(9%)
E.	Increased	Increased	Decreased	Increased	(17%)

Incorrect
Correct answer
B

55%
Answered correctly

03 secs
Time Spent

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Explanation

Common causes of primary acid-base disturbance

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Explanation

Common causes of primary acid-base disturbance	
Metabolic acidosis	**Elevated anion gap** • Poor tissue perfusion (ie, lactic acidosis) • Diabetic ketoacidosis • Renal failure (ie, uremia) • Certain toxicities (eg, methanol, ethylene glycol) **Normal anion gap** • Severe diarrhea • Renal tubular acidosis • Excess normal saline infusion
Metabolic alkalosis	• Nasogastric suctioning or severe vomiting • Diuretic overuse • Primary hyperaldosteronism
Respiratory acidosis (hypoventilation)	• Central respiratory depression (eg, opioid overdose) • OHS, neuromuscular weakness • Chronic obstructive pulmonary disease
Respiratory alkalosis (hyperventilation)	• Acute V/Q mismatch (eg, PE, pneumonia) • Anxiety, inadequate pain control • High altitude, pregnancy

OHS = obesity hypoventilation syndrome; **PE** = pulmonary embolism; **V/Q** = ventilation/perfusion.

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OHS = obesity hypoventilation syndrome; **PE** = pulmonary embolism; **V/Q** = ventilation/perfusion.

This patient likely has **nonanion gap metabolic acidosis** (NAGMA) due to **infusion of excess normal saline**. Excess sodium chloride increases serum chloride (Cl^-) to cause **hyperchloremia**. Because Cl^- and bicarbonate (HCO_3^-) are the predominant anions in the body, the increased serum Cl^- causes intracellular shifting of HCO_3^- to maintain electronegative balance. This "loss" of HCO_3^- (**reduced serum HCO_3^-**) decreases blood pH. Infusion of excess normal saline also increases intravascular volume, which the kidneys respond to by increasing sodium (Na^+) excretion, resulting in **increased urine Na^+**.

Other causes of NAGMA usually involve loss of HCO_3^- from the kidneys (eg, renal tubular acidosis) or gastrointestinal tract (eg, severe diarrhea). With these etiologies, serum Cl^- is increased to compensate for the loss of HCO_3^-. Because of the inverse relationship between Cl^- and HCO_3^-, NAGMA of any etiology is also referred to as **hyperchloremic acidosis**.

(Choice A) Metabolic acidosis with hypochloremia (decreased serum HCO_3^-, pH, and serum Cl^-) can occur with diabetic ketoacidosis. The typical inverse relationship between serum HCO_3^- and Cl^- is disrupted due to the presence of unmeasured anions (ie, ketones) in the blood and profound Cl^- losses from osmotic diuresis (due to glucosuria). Urine Na^+ is low due to hypovolemia and consequent increased aldosterone-mediated urinary Na^+ reabsorption.

(Choice C) Increased serum HCO_3^- does not explain decreased pH (acidemia), but the combination of the two can occur with metabolic compensation for primary respiratory acidosis (eg, chronic hypoventilation). Serum Cl^- is decreased in response to the increase in serum HCO_3^-. Urine Na^+ is unchanged in the absence of a change in volume status.

(Choices D and E) Hypochloremic metabolic alkalosis (decreased serum Cl^-, increased serum HCO_3^- and pH) can occur in the setting of hypovolemia (eg, poor oral intake/vomiting, diuretic overuse) or hypervolemia (eg, primary hyperaldosteronism). Urine Na^+ is decreased with hypovolemic etiologies and increased with hypervolemic

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(Na^+) excretion, resulting in **increased urine Na^+**.

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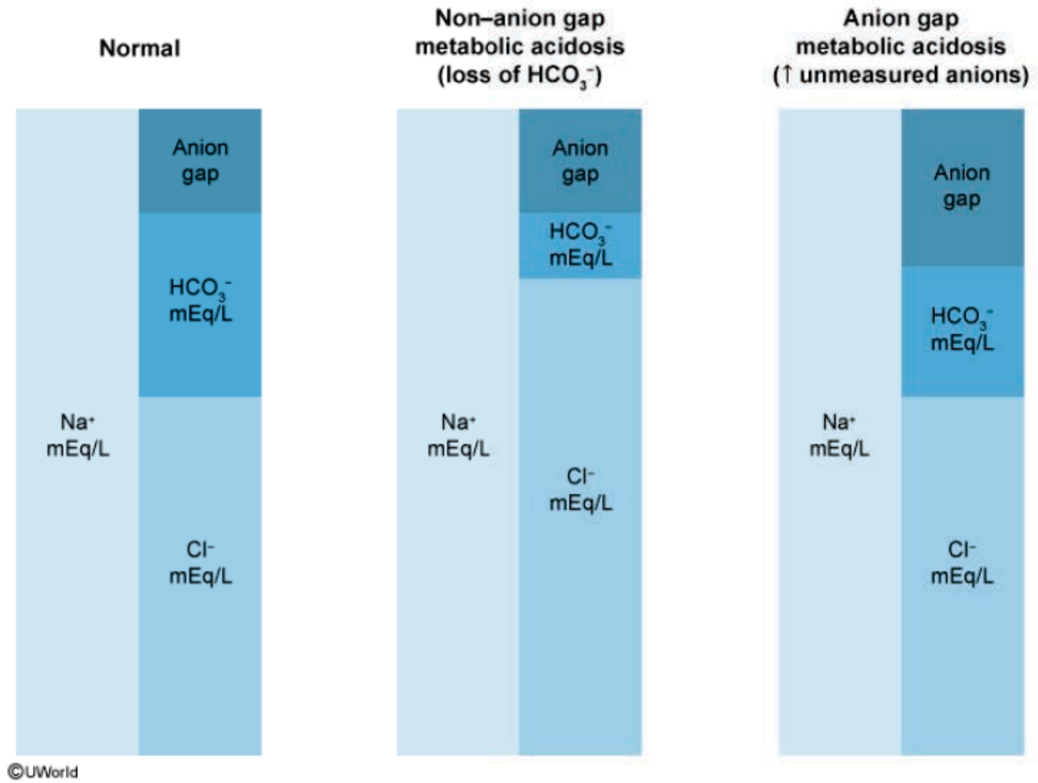
Educational objective:
The infusion of excessive normal saline (sodium chloride) is a common cause of nonanion gap metabolic acidosis. The excess intravascular chloride (Cl^-) causes intracellular shifting of bicarbonate (HCO_3^-), reducing serum HCO_3^- and decreasing blood pH.

References

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Respiratory acidosis (hypoventilation)	• OHS, neuromuscular weakness

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A 5-year-old girl is brought to the clinic due to 2 days of dark red urine. The patient was treated for facial impetigo a month ago. Blood pressure is 140/90 mm Hg. Urinalysis reveals hematuria, mild proteinuria, and occasional red blood cell casts. Which of the following glomerular changes are most likely to be present within this patient's kidneys?

- A. Diffuse capillary wall thickening on light microscopy
- B. Discrete subepithelial humps on electron microscopy
- C. Glomerular basement membrane rupture on electron microscopy
- D. Glomerular basement membrane splitting on light microscopy
- E. Linear IgG and C3 deposits on immunofluorescent microscopy

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- A. Diffuse capillary wall thickening on light microscopy (3%)
- ✓ B. Discrete subepithelial humps on electron microscopy (65%)
- C. Glomerular basement membrane rupture on electron microscopy (3%)
- D. Glomerular basement membrane splitting on light microscopy (3%)
- E. Linear IgG and C3 deposits on immunofluorescent microscopy (24%)

Correct

65% Answered correctly

03 secs Time Spent

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Explanation

Pathologic findings in nephritic syndrome

	Cause of glomerular injury	Characteristic biopsy features
Poststreptococcal glomerulonephritis	Antibodies against streptococcal antigens that deposit in GBM	• IF: C3 granular staining along GBM • EM: subepithelial humps
Anti-GBM disease	Antibodies against type IV collagen in GBM	• LM: glomerular crescents • IF: linear staining (IgG) along GBM

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Anti-GBM disease	Antibodies against type IV collagen in GBM	• LM: glomerular crescents • IF: linear staining (IgG) along GBM
Rapidly progressive glomerulonephritis	Severe immunologic injury (eg, anti-GBM antibodies, immune complex deposition)	• LM: glomerular crescents • IF: fibrin in crescents
IgA nephropathy	Deposition of IgA-containing complexes	• LM: mesangial hypercellularity • IF: IgA in mesangium
Alport syndrome	Defective type IV collagen in GBM	• EM: lamellated appearance of GBM
EM = electron microscopy; **GBM** = glomerular basement membrane; **IF** = immunofluorescence; **LM** = light microscopy.		

This patient has **nephritic syndrome**, which is characterized by hypertension, mild proteinuria, and hematuria with red blood cell casts in the urine sediment. In association with a recent skin infection, this presentation suggests **poststreptococcal glomerulonephritis** (PSGN), the most common cause of nephritic syndrome in children.

PSGN is an **immune complex–mediated** disease that occurs 2-4 weeks after exposure to group A beta-hemolytic *Streptococcus* (eg, pharyngitis, skin infection). Antigens expressed on nephritogenic streptococcal species combine with antibodies to form immune complexes, which later deposit in the glomerular basement membrane (GBM).

On light microscopy, glomeruli are enlarged and hypercellular due to leukocyte infiltration and proliferation of endothelial and mesangial cells. On electron microscopy, **electron-dense deposits** (humps) on the **epithelial**

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On light microscopy, glomeruli are enlarged and hypercellular due to leukocyte infiltration and proliferation of endothelial and mesangial cells. On electron microscopy, **electron-dense deposits** (humps) on the **epithelial** side of the GBM are seen. Immunofluorescence shows coarse, **granular** deposits of **IgG and C3** that have a characteristic "lumpy-bumpy" appearance.

(Choice A) Uniform, diffuse thickening of glomerular capillary walls on light microscopy is characteristic of membranous nephropathy, one of the most common causes of nephrotic syndrome in adults. Manifestations of nephrotic syndrome include generalized edema, marked proteinuria (>3.5 g/day), hypoalbuminemia, hyperlipidemia, and lipiduria.

(Choices C and E) In contrast to PSGN, which demonstrates granular deposits of IgG and C3 along the GBM, linear IgG and C3 deposits are characteristic of Goodpasture syndrome (anti-GBM disease). This commonly presents with rapidly progressive glomerulonephritis (RPGN), in which severe damage leads to GBM rupture and leakage of plasma proteins into the Bowman space, resulting in fibrin deposition and parietal cell proliferation (crescent formation). PSGN rarely progresses to RPGN.

(Choice D) GBM splitting is seen in membranoproliferative glomerulonephritis (MPGN) and Alport syndrome. Alport syndrome causes nephritic syndrome but is most commonly X-linked and therefore more common in male patients; it is not associated with recent streptococcal infections. Although MPGN may cause hematuria and proteinuria, PSGN is more common in children.

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On light microscopy, glomeruli are enlarged and hypercellular due to leukocyte infiltration and proliferation of endothelial and mesangial cells. On electron microscopy, **electron-dense deposits** (humps) on the **epithelial** side of the GBM are seen. Immunofluorescence shows coarse, **granular** deposits of **IgG and C3** that have a characteristic "lumpy-bumpy" appearance.

(Choice A) Uniform, diffuse thickening of glomerular capillary walls on light microscopy is characteristic of membranous nephropathy, one of the most common causes of nephrotic syndrome in adults. Manifestations of nephrotic syndrome include generalized edema, marked proteinuria (>3.5 g/day), hypoalbuminemia, hyperlipidemia, and lipiduria.

(Choices C and E) In contrast to PSGN, which demonstrates granular deposits of IgG and C3 along the GBM, linear IgG and C3 deposits are characteristic of Goodpasture syndrome (anti-GBM disease). This commonly presents with rapidly progressive glomerulonephritis (RPGN), in which severe damage leads to GBM rupture and leakage of plasma proteins into the Bowman space, resulting in fibrin deposition and parietal cell proliferation (crescent formation). PSGN rarely progresses to RPGN.

(Choice D) GBM splitting is seen in membranoproliferative glomerulonephritis (MPGN) and Alport syndrome. Alport syndrome causes nephritic syndrome but is most commonly X-linked and therefore more common in male patients; it is not associated with recent streptococcal infections. Although MPGN may cause hematuria and proteinuria, PSGN is more common in children.

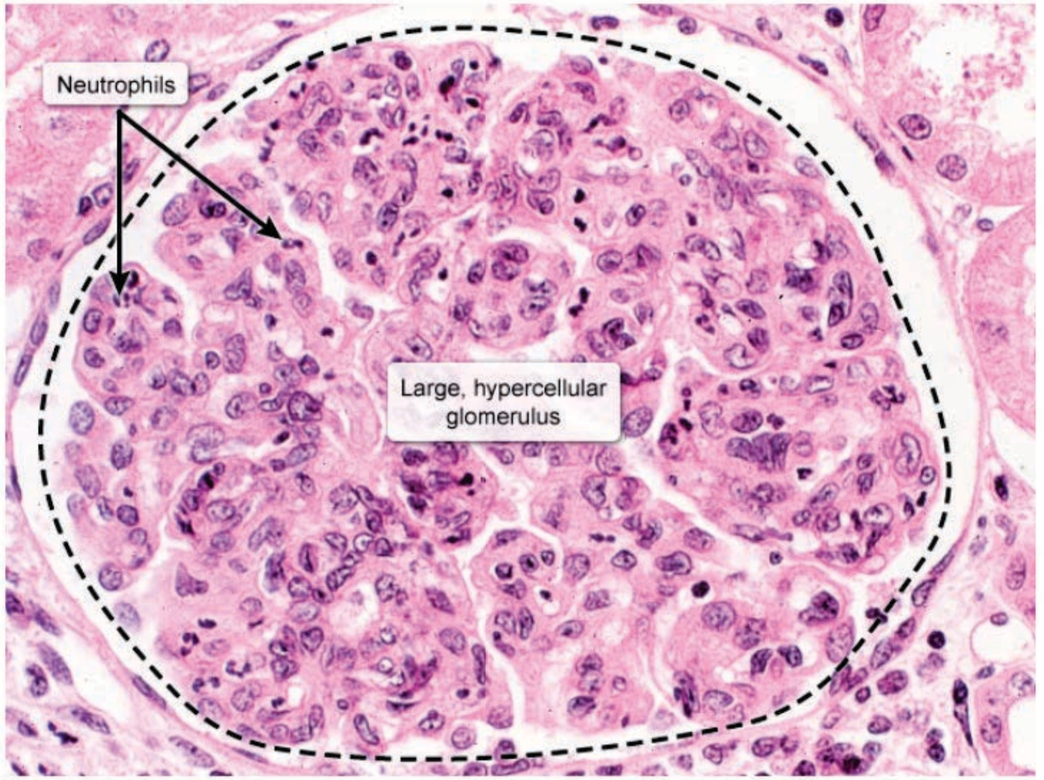
Educational objective:
Poststreptococcal glomerulonephritis is an immune complex–deposition disease that occurs 2-4 weeks after exposure to group A beta-hemolytic *Streptococcus* species (eg, pharyngitis, skin infection). Light microscopy shows enlarged, hypercellular glomeruli. Immunofluorescence demonstrates "lumpy-bumpy" granular deposits of IgG and C3 on the glomerular basement membrane, and subepithelial, electron-dense deposits are seen on electron microscopy.

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Rapidly progressive	Severe immunologic injury (eg, anti-GBM antibodies, immune complex	• LM: glomerular crescents

Exhibit Display

Poststreptococcal glomerulonephritis



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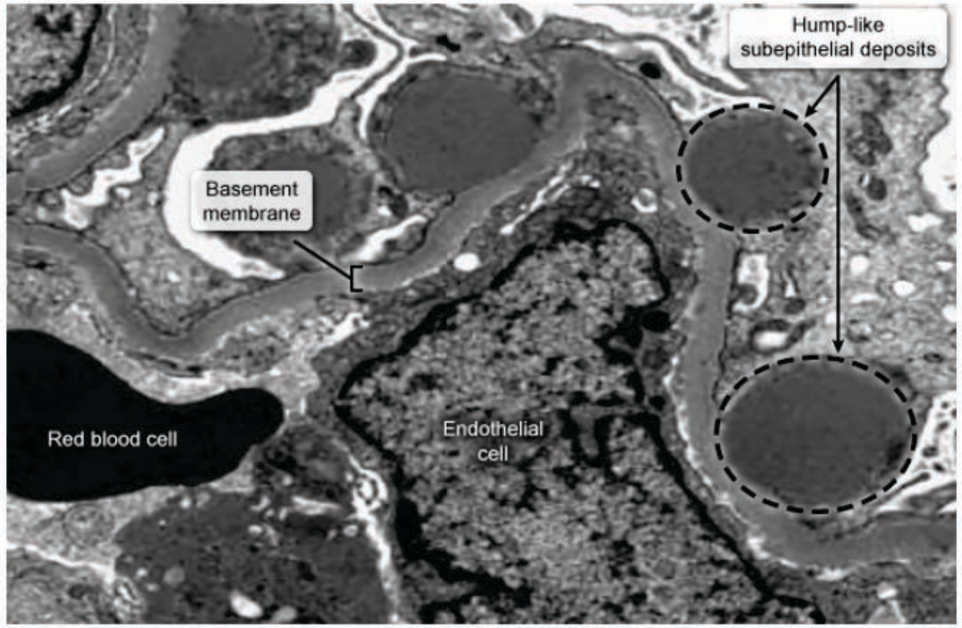
(Choices C and E) In contrast to PSGN, which demonstrates granular deposits of IgG and C3 along the GBM,

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Rapidly progressive	Severe immunologic injury (eg, anti-GBM antibodies, immune complex	• LM: glomerular crescents

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Poststreptococcal glomerulonephritis



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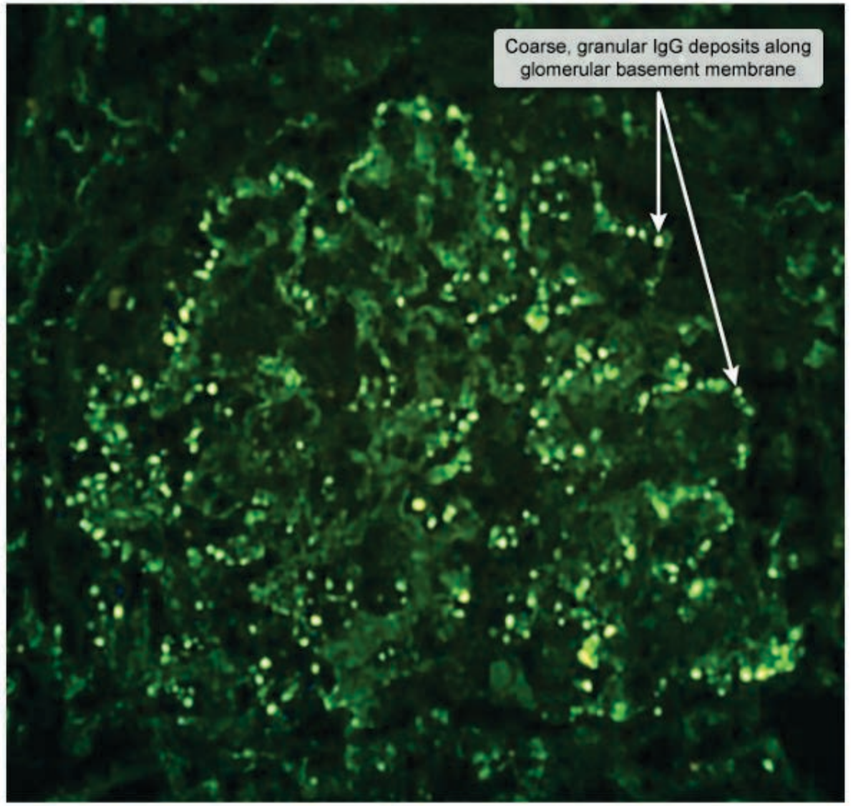
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Rapidly progressive	Severe immunologic injury (eg, anti-GBM antibodies, immune complex	• LM: glomerular crescents

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Poststreptococcal glomerulonephritis



Immunofluorescence

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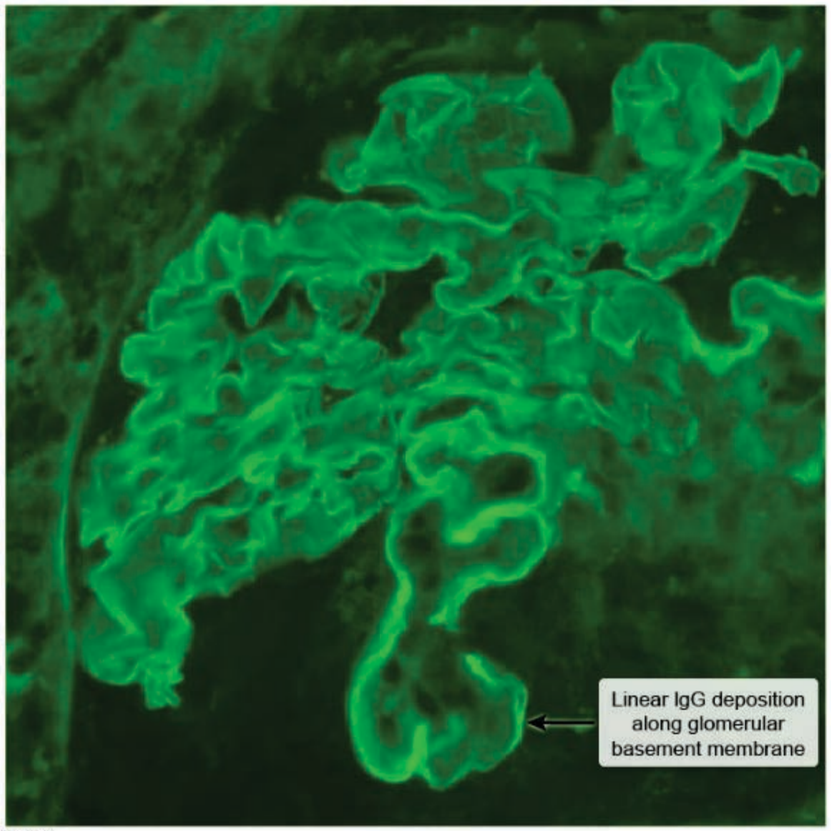
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exposure to group A beta-hemolytic *Streptococcus* species (eg, pharyngitis, skin infection). Light microscopy shows enlarged, hypercellular glomeruli. Immunofluorescence demonstrates "lumpy-bumpy" granular deposits of

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Anti-glomerular basement membrane disease



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A 67-year-old woman is hospitalized due to worsening abdominal pain. The patient has long-standing end-stage renal disease from diabetic nephropathy for which she undergoes hemodialysis 3 times a week. Temperature is 37 C (98.6 F), blood pressure is 159/79 mm Hg, pulse is 97/min, and respirations are 16/min. Abdominal examination shows high-pitched bowel sounds and mild distension without rebound tenderness. Laboratory results show elevated blood urea nitrogen and creatinine. Noncontrast CT scan of the abdomen shows a small bowel obstruction. The patient also has the findings demonstrated by the arrows in the abdominal CT scan below:

Which of the following most likely contributed to the observed findings?

- A. Hypermagnesemia
- B. Hyperphosphatemia
- C. Hypocalcemia
- D. Hypophosphatemia
- E. Recurrent hypoglycemia

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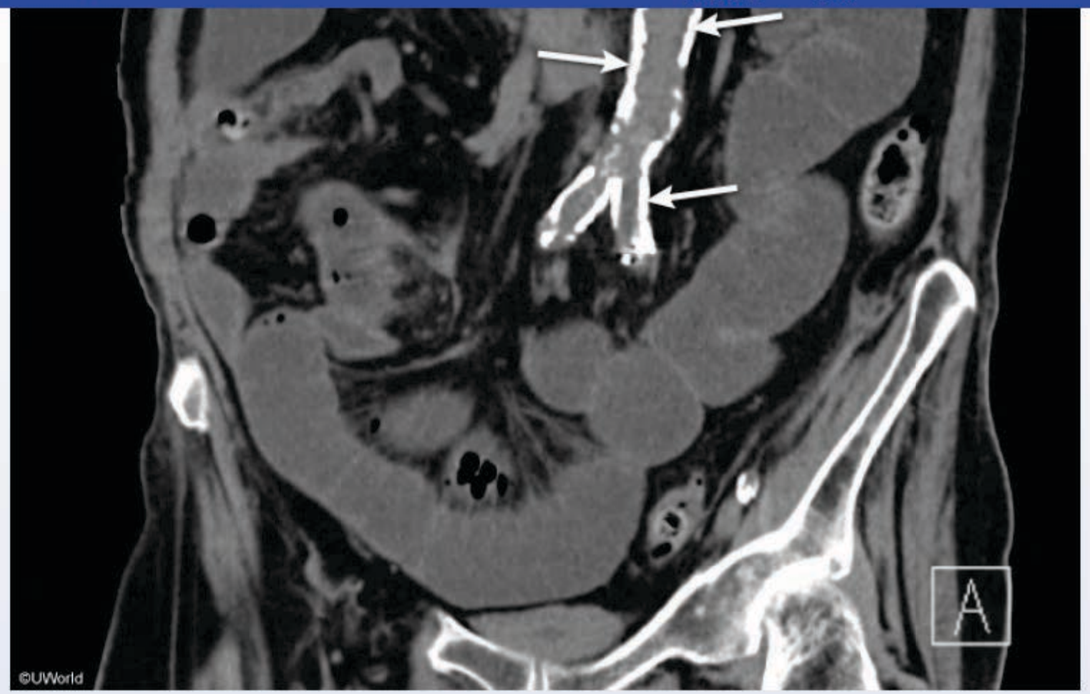
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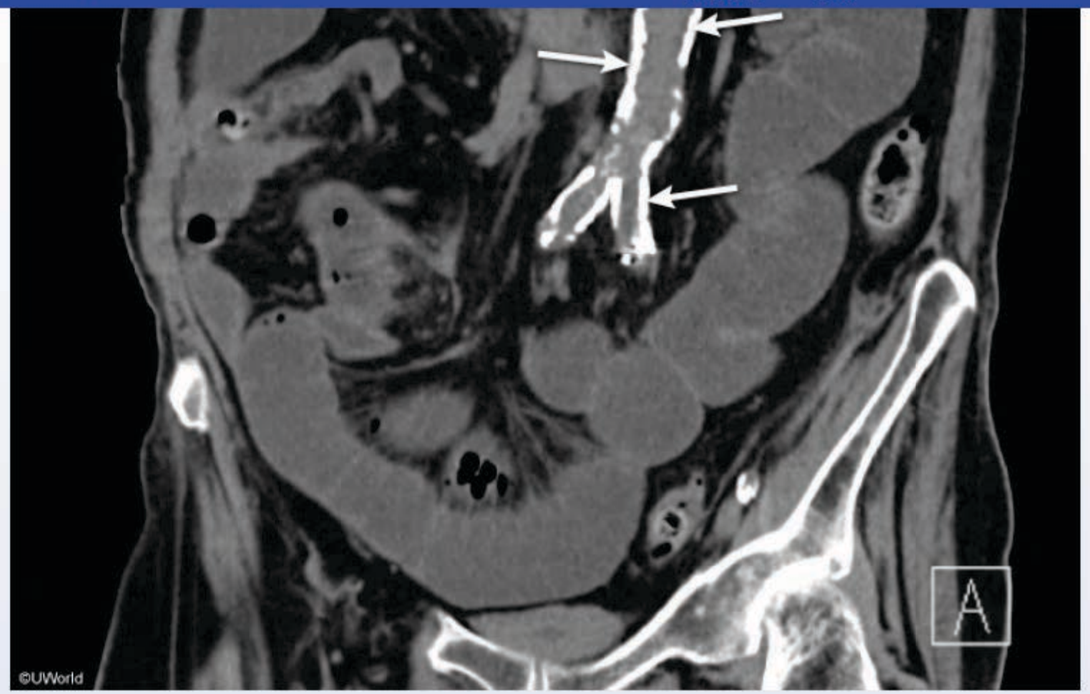


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- A. Hypermagnesemia
- B. Hyperphosphatemia
- C. Hypocalcemia
- D. Hypophosphatemia
- E. Recurrent hypoglycemia

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Which of the following most likely contributed to the observed findings?

- A. Hypermagnesemia (4%)
- ✓ B. Hyperphosphatemia (67%)
- C. Hypocalcemia (6%)
- D. Hypophosphatemia (20%)
- E. Recurrent hypoglycemia (1%)

Correct

67%
Answered correctly

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Explanation

This patient with end-stage renal disease (due to diabetic nephropathy) and worsening abdominal pain (due to small bowel obstruction) has extensive **vascular calcifications** (VCs) noted on abdominal CT scan. Under normal conditions, calcification inhibitors expressed by smooth muscle cells prevent the formation of calcifications. VCs occur when metabolic insults (eg, electrolyte abnormalities, dyslipidemia, oxidative stress, uremia) cause smooth muscle cells in the arterial media to differentiate into osteoblast-like cells (ie, **osteogenic differentiation**), resulting in active deposition of calcium salts within the vessels.

Excessive VCs occur frequently in patients with **chronic kidney disease**, especially those on **dialysis**, because they are predisposed to developing these calcifications through the following mechanisms:

- Electrolyte abnormalities: **Hyperphosphatemia** (decreased filtration and excretion of phosphorus) and/or **hypercalcemia** (typically iatrogenic due to the administration of calcium products as phosphate binders) promote calcification by stimulating osteogenic differentiation **(Choices C and D)**.
- **Chronic inflammation**: Inflammation, due to uremia and/or hyperlipidemia, suppresses the expression of calcification inhibitors in smooth muscle cells and damages vascular endothelial cells, providing a nidus for calcification. In addition, mineralization is proinflammatory and reinforces the cycle of inflammation within vessel walls.
- **Atherosclerosis**: In addition to its proinflammatory effects, lipid deposition in the vessel wall results in the formation of atherosclerotic lesions that can also become calcified and contribute to the calcific burden.

VCs are thought to contribute to increased cardiovascular risk and mortality but are often an **incidental finding**.

(Choice A) Magnesium inhibits extraosseous calcification, putting those with hypomagnesemia at increased risk for VCs. Hypermagnesemia would have a protective effect, making VCs less likely.

(Choice E) Diabetes mellitus is associated with a significantly increased risk for atherosclerosis and subsequent

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VCs are thought to contribute to increased cardiovascular risk and mortality but are often an **incidental finding**.

(Choice A) Magnesium inhibits extraosseous calcification, putting those with hypomagnesemia at increased risk for VCs. Hypermagnesemia would have a protective effect, making VCs less likely.

(Choice E) Diabetes mellitus is associated with a significantly increased risk for atherosclerosis and subsequent atherosclerotic calcification. However, hypoglycemia does not increase the risk for VCs.

Educational objective:
Vascular calcifications occur more commonly in patients with chronic kidney disease due to electrolyte abnormalities (eg, hyperphosphatemia, hypercalcemia) and chronic inflammation (secondary to atherosclerosis and/or uremia). These changes promote calcification and suppress calcification inhibitors, which can result in extensive vascular calcifications.

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A 34-year-old primigravida at 18 weeks gestation comes to the office for a routine prenatal examination. The patient's pregnancy has been uncomplicated. She takes a prenatal vitamin daily, and her laboratory results have been normal to date. The patient's personal and family medical histories are unremarkable. During the visit, a detailed fetal ultrasound examination reveals severe unilateral hydronephrosis; there is no ureteral dilation. Male external genitalia are also visible. If the fetal hydronephrosis is caused by obstruction, which of the following is the most likely site?

- A. Spinal cord
- B. Ureteropelvic junction
- C. Urethra
- D. Urinary meatus
- E. Vesicoureteral junction

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- A. Spinal cord (1%)
- ✓ B. Ureteropelvic junction (65%)
- C. Urethra (4%)
- D. Urinary meatus (2%)
- E. Vesicoureteral junction (25%)

Correct

65%
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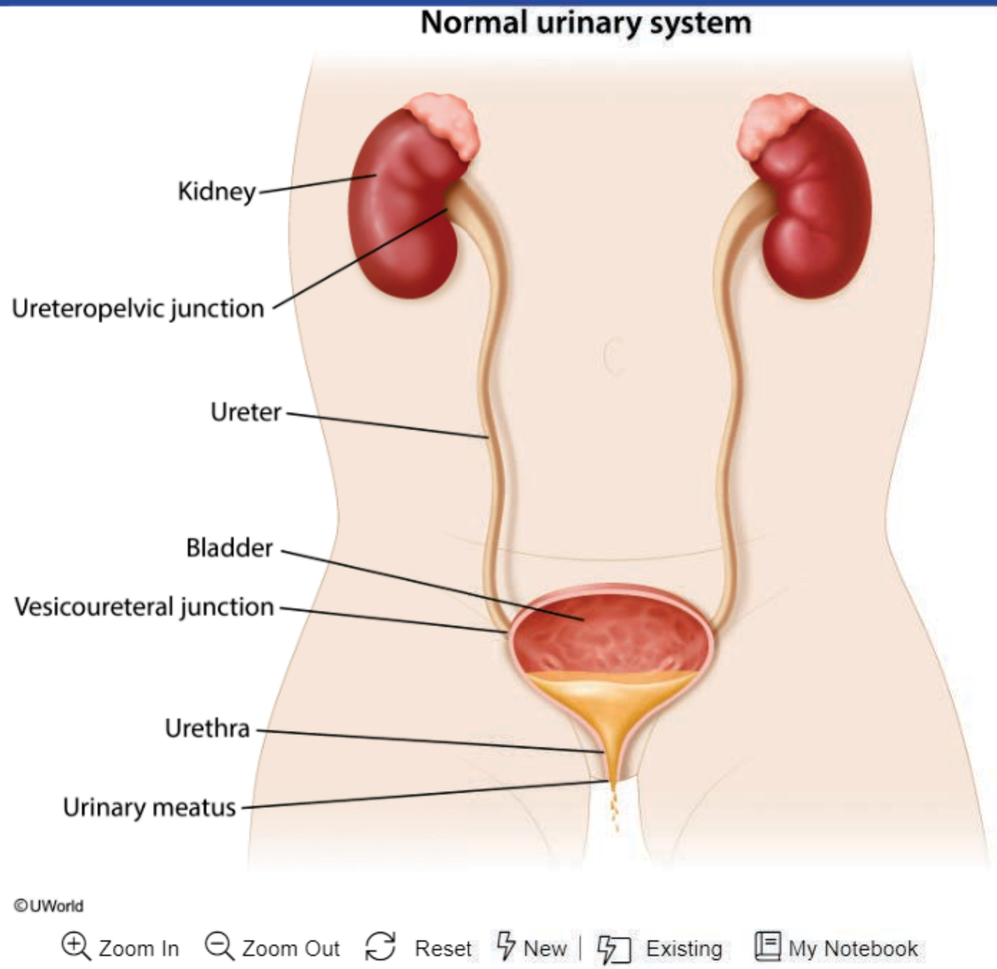
Explanation



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A 34-year-old primigravida at 18 weeks gestation comes to the office for a routine prenatal examination. The patient has been detailed extensively about the most

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Fetal hydronephrosis is a common finding on routine ultrasound examination during the second trimester. The finding is most commonly **unilateral**, mild, and transient, likely related to a temporary narrowing in the **ureteropelvic junction** (UPJ) during normal development, as the fetal renal pelvis is highly compliant and susceptible to dilation. In this case, however, the dilation is severe, making a pathologic cause more likely.

The most common pathologic cause of antenatal hydronephrosis is persistent UPJ **obstruction** due to an embryologic defect that develops as follows:

- The fetal genitourinary tract is derived from the metanephric blastema and the ureteric bud (a dorsal outgrowth of the mesonephric duct). The metanephric blastema develops into functional renal parenchyma by 10 weeks gestation while the ureteric bud develops into the renal pelvis and ureters through sequential dilation and canalization. The UPJ is the last segment of the fetal ureter to canalize.
- The pathogenesis of fetal UPJ obstruction likely involves **canalization failure** resulting in stenosis of the proximal ureter. Most cases are unilateral and cause hydronephrosis with calyceal/renal pelvic dilation and without ureteral dilation. If the condition is not diagnosed prenatally, it may present with a palpable abdominal mass (enlarged kidney) on examination.

(Choice A) Neurogenic causes of obstructive uropathy (eg, spinal cord damage) result in *bilateral* hydronephrosis along with hydroureter due to dysfunctional voiding.

(Choices C and D) Obstruction of the urethra or urinary meatus causes *bilateral*, not unilateral, hydronephrosis in addition to ureteral dilation. The most common cause in boys is posterior urethral valves or obstructive urogenital membranes at the junction of the bladder and urethra. Other congenital anomalies at this anatomic level that would also cause bilateral fetal hydronephrosis include urethral strictures, meatal stenosis, and bladder neck obstruction.

(Choice E) Abnormalities at the vesicoureteral junction (eg, congenital anomaly, renal calculi) can cause obstruction but are rare and would lead to *ureteral dilation* (not seen here) if severe enough to cause

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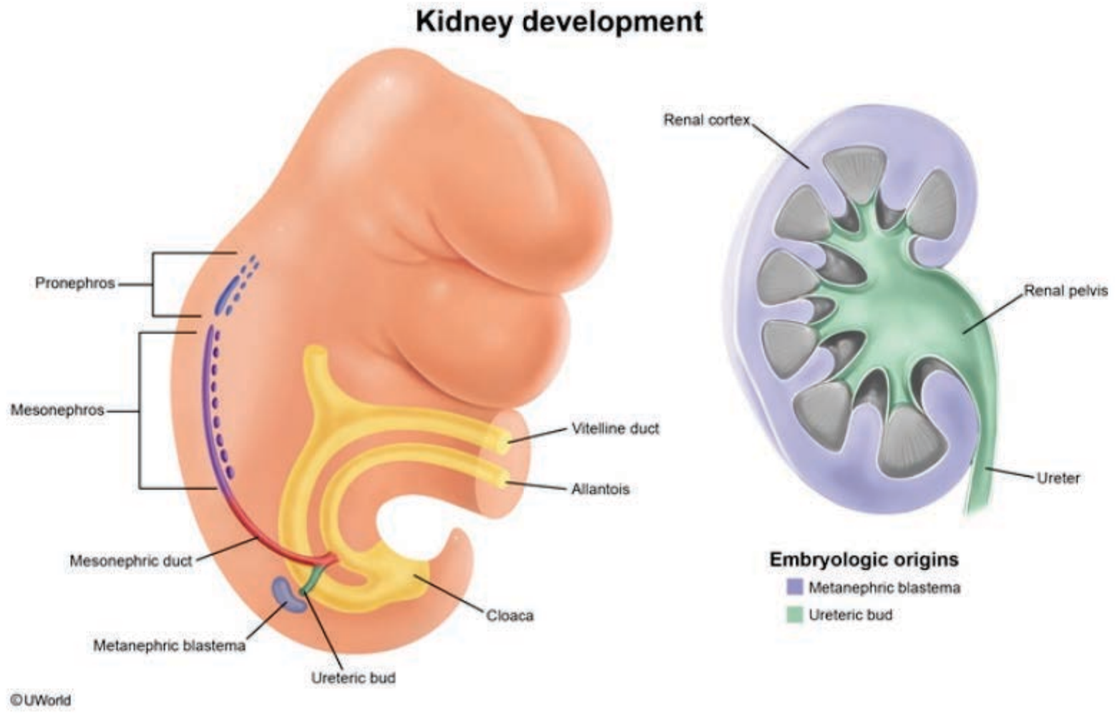
(Choice E) Abnormalities at the vesicoureteral junction (eg, congenital anomaly, renal calculi) can cause obstruction but are rare and would lead to *ureteral dilation* (not seen here) if severe enough to cause hydronephrosis. Similarly, vesicoureteral reflux (VUR), a common cause of fetal hydronephrosis, is also associated with ureteral dilation/tortuosity.

Educational objective:
Inadequate canalization of the ureter at the ureteropelvic junction (the connection site between the kidney and the ureter) is the most common cause of severe, unilateral fetal hydronephrosis.

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Urinary meatus

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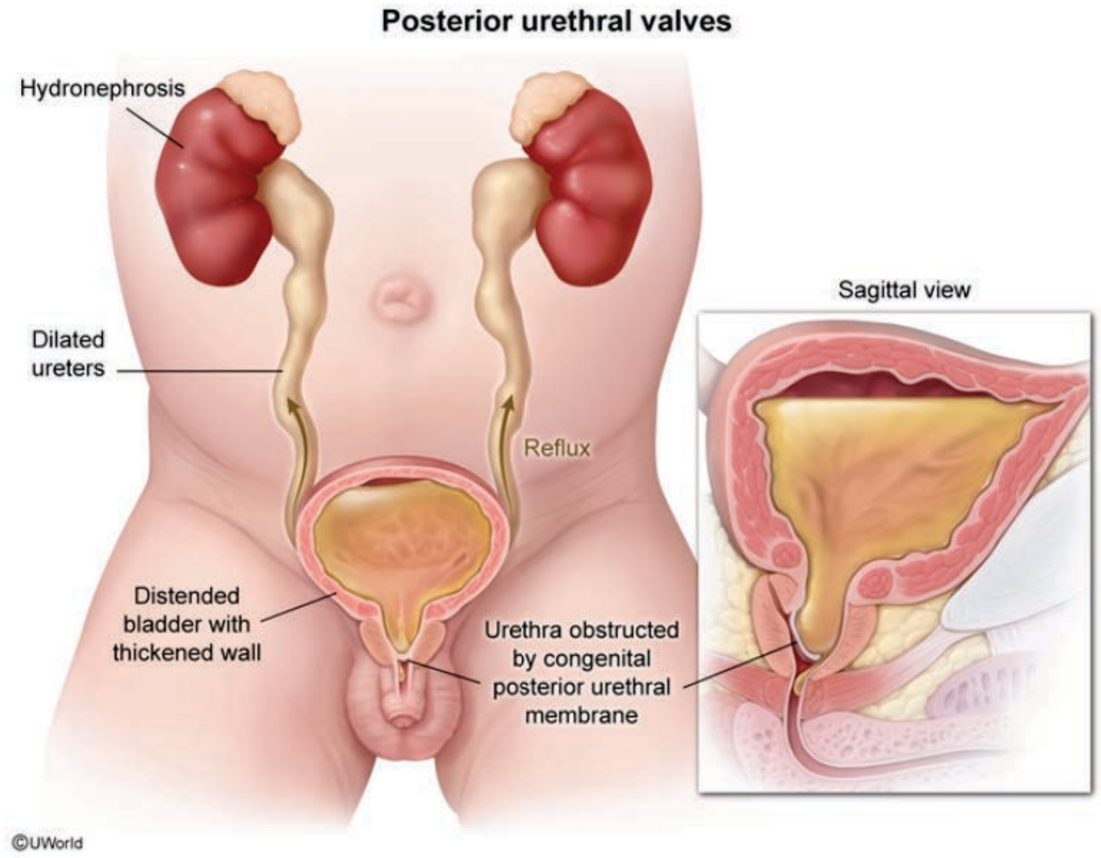
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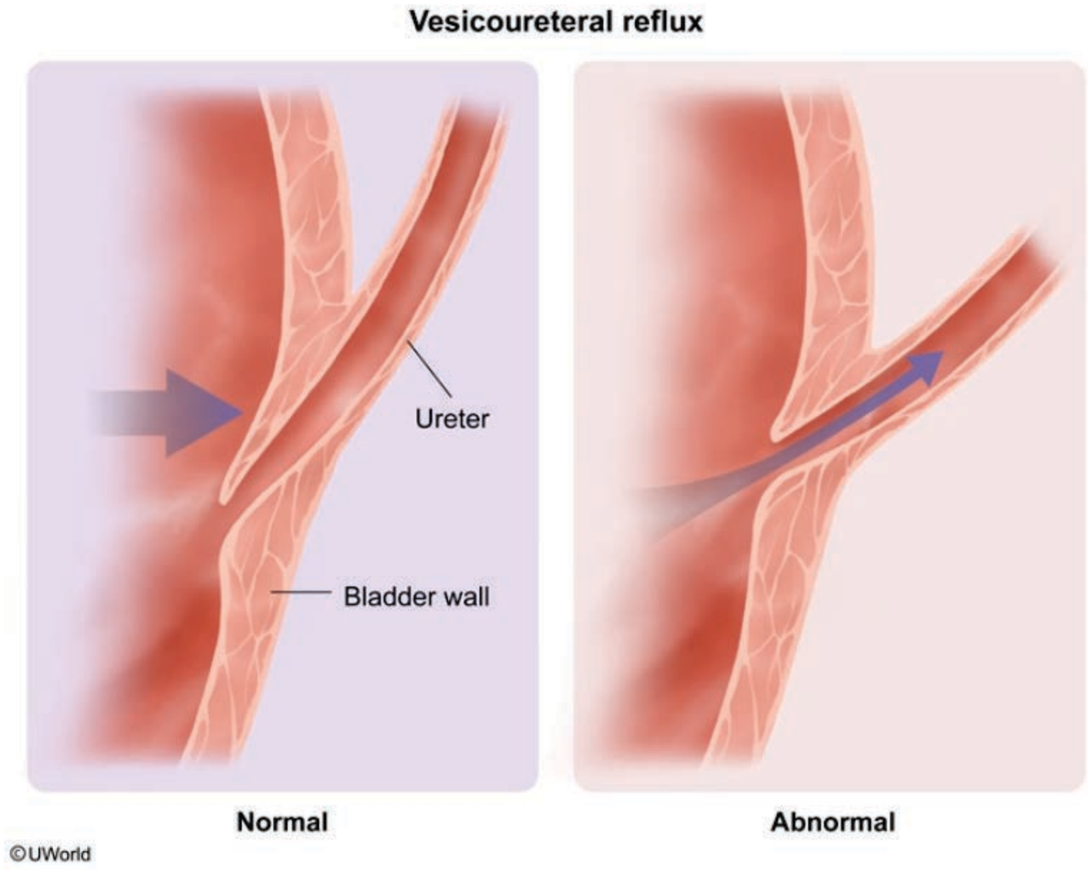


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10 weeks gestation while the ureteric bud develops into the renal pelvis and ureters through sequential

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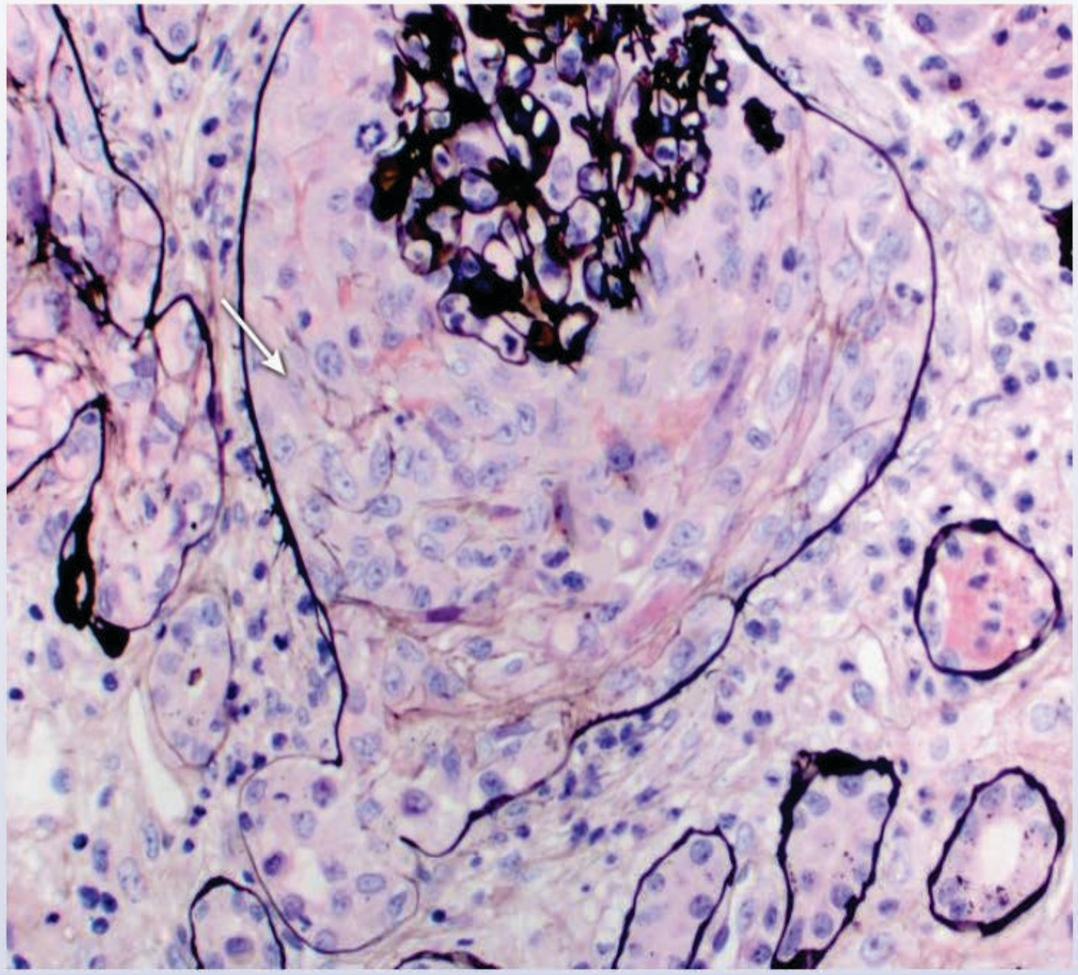


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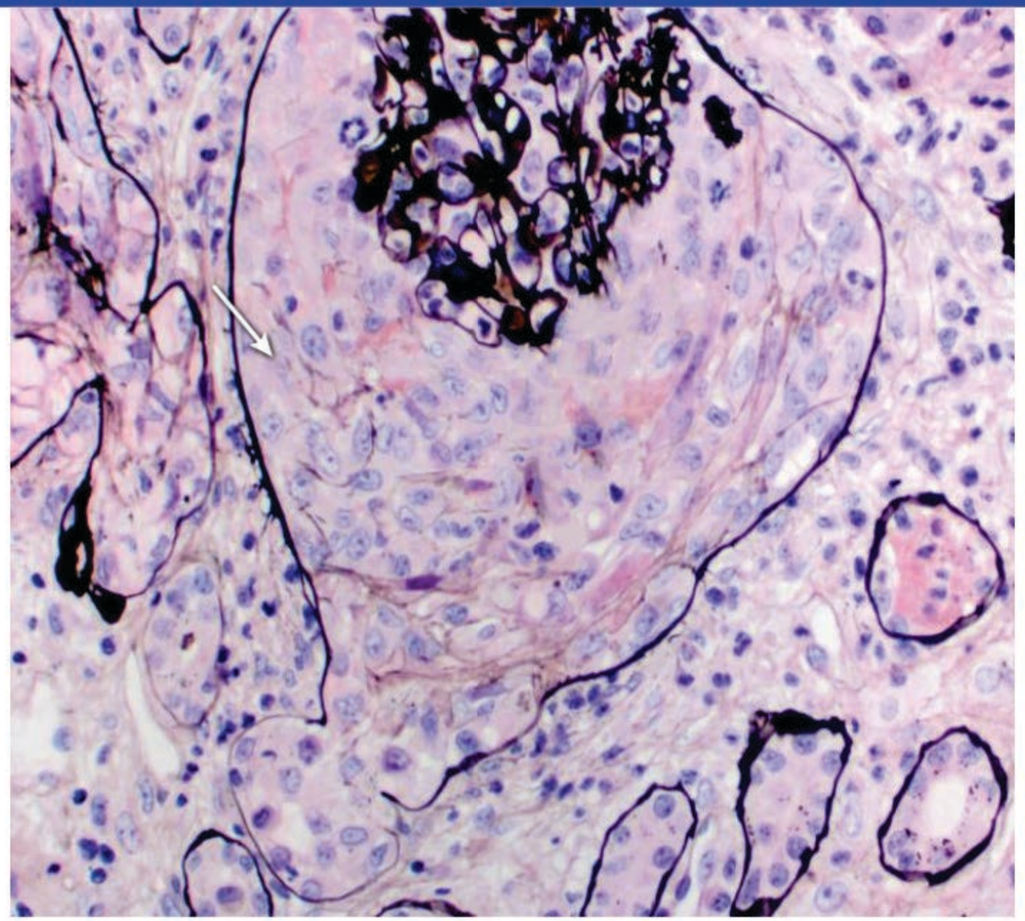
A 34-year-old man is being evaluated for acute hematuria and oliguria. He has no chronic medical conditions and takes no medications on a regular basis. Blood pressure is 170/100 mm Hg. Blood urea nitrogen is 38 mg/dL and serum creatinine is 4.5 mg/dL. The patient undergoes a kidney biopsy and the following microscopic changes are seen after silver staining to highlight the glomerular tuft:



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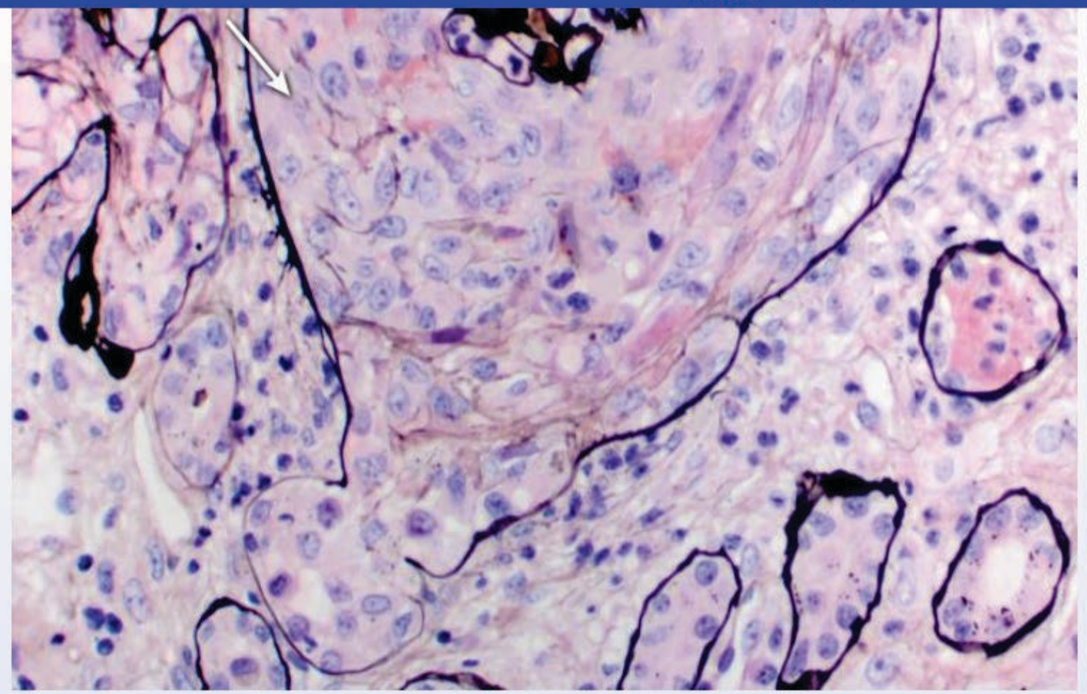
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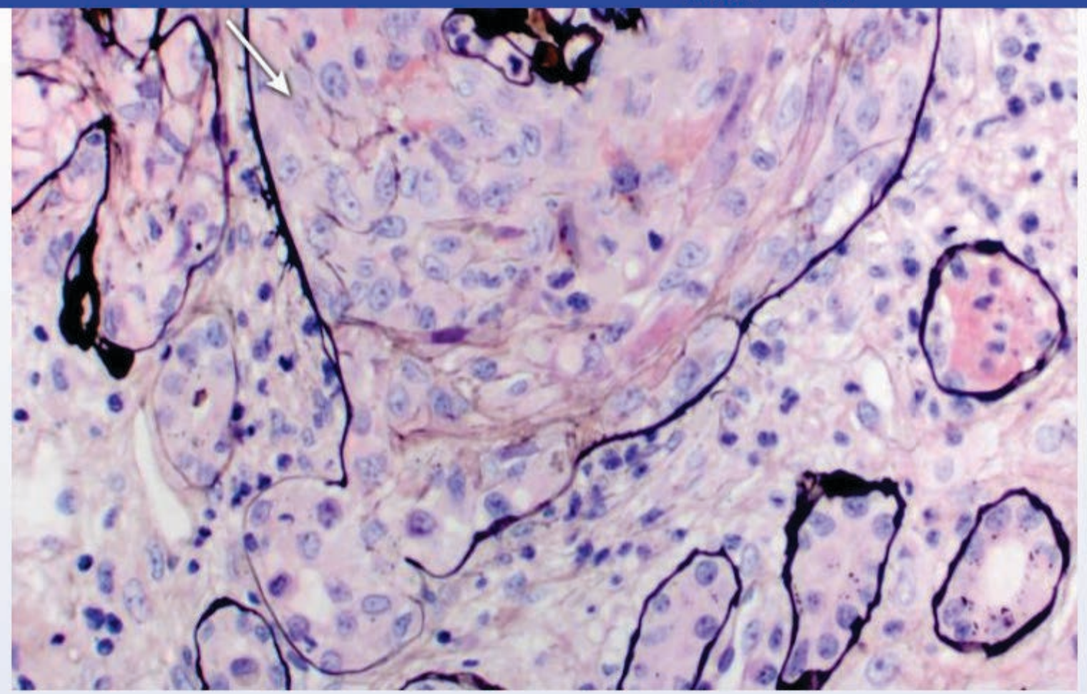


The area marked with an arrow is likely to have abnormal deposition of which of the following substances?

- A. Amyloid
- B. Fibrin
- C. IgE
- D. Lipid
- E. Myoglobin

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The area marked with an arrow is likely to have abnormal deposition of which of the following substances?

- A. Amyloid (21%)
- ✓ B. Fibrin (65%)
- C. IgE (4%)
- D. Lipid (2%)
- E. Myoglobin (6%)

Correct

65% Answered correctly

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Explanation

This patient with acute renal failure and hematuria has a glomerular crescent, defined as >2 layers of **proliferating cells within Bowman's space**. Glomerular crescent formation occurs in response to immune or inflammatory-mediated injury to glomerular capillaries. Disruption of the glomerular basement membrane allows gaps to form within the capillary, resulting in an influx of coagulation factors (eg, fibrinogen) and inflammatory cells (eg, lymphocytes, macrophages) into Bowman's space. Initiation of the coagulation cascade promotes the deposition of **large quantities of fibrin**, while inflammatory cells proliferate and release growth factors and inflammatory cytokines that recruit fibroblasts and stimulate parietal cell proliferation. This eventually results in progressive glomerular hypercellularity, fibrosis, and irreversible renal injury.

Crescent formation is diagnostic of **rapidly progressive glomerulonephritis** (RPGN), a syndrome of severe renal injury that can occur in a number of disease processes (eg, anti-glomerular basement antibody [Goodpasture] disease, granulomatosis with polyangiitis). Like other nephritic syndromes, it typically presents with hematuria, hypertension, and progressive renal failure; however, renal decompensation and progression to end-stage renal disease occur particularly quickly (weeks to months) in RPGN.

(Choice A) Amyloid is visualized as amorphous deposits on light microscopy or, when stained with Congo red, as apple-green, birefringent deposits under polarized light. It is associated with nephrotic syndrome (heavy proteinuria, hyperlipidemia), not with nephritic syndrome as seen in this patient.

(Choice C) Goodpasture disease can cause RPGN and is characterized by antibodies against the glomerular basement membrane. However, these antibodies are usually IgG, or occasionally IgM or IgA. In contrast, IgE antibodies mediate immediate hypersensitivity reactions and are involved in defense against certain parasites.

(Choice D) The clear cells seen in renal cell carcinoma (RCC) have a high lipid content, which is responsible for the yellow tinge noted on gross examination. RCC can cause hematuria and hypertension but does not cause crescent formation or renal failure.

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glomerular hypercellularity, fibrosis, and irreversible renal injury.

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(Choice D) The clear cells seen in renal cell carcinoma (RCC) have a high lipid content, which is responsible for the yellow tinge noted on gross examination. RCC can cause hematuria and hypertension but does not cause crescent formation or renal failure.

(Choice E) Myoglobinuria is seen in rhabdomyolysis; urine dipstick is positive for blood, but red blood cells are absent on urinalysis. Myoglobin is toxic to renal tubular cells and induces acute tubular necrosis, not glomerular injury and crescent formation.

Educational objective:
Crescent formation on light microscopy is diagnostic for rapidly progressive glomerulonephritis. Crescents consist of glomerular parietal cells, lymphocytes, and macrophages along with abundant fibrin deposition. Crescents eventually become fibrotic, disrupting glomerular function and causing irreversible renal injury.

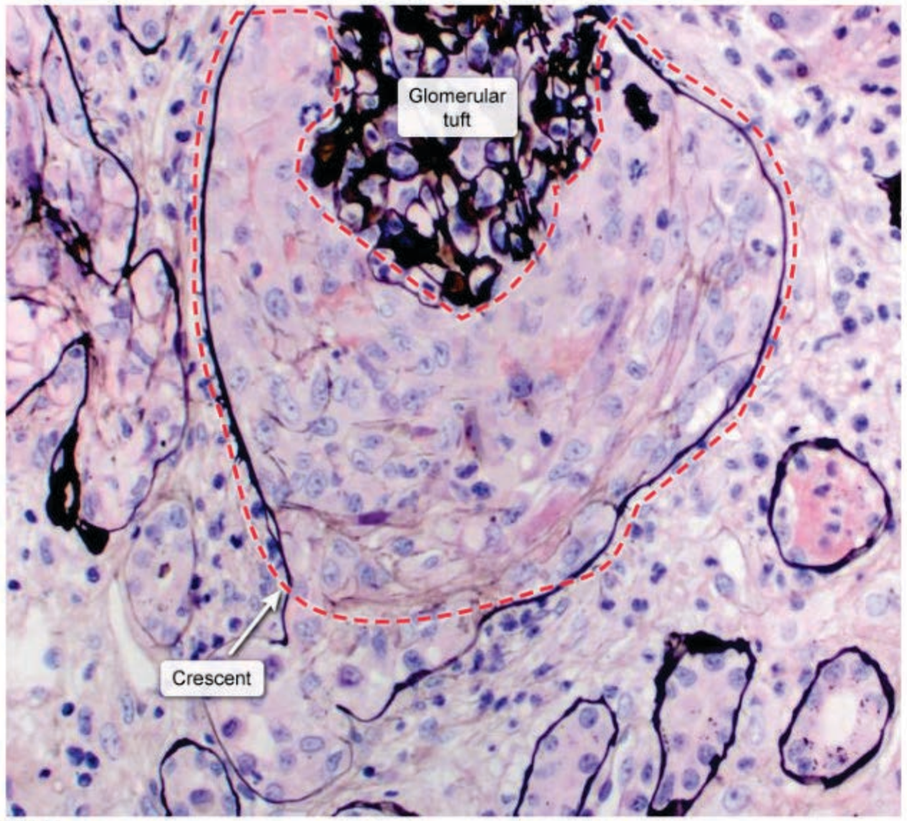
Pathology | Renal, Urinary Systems & Electrolytes | Glomerular disorders

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Crescentic glomerulonephritis



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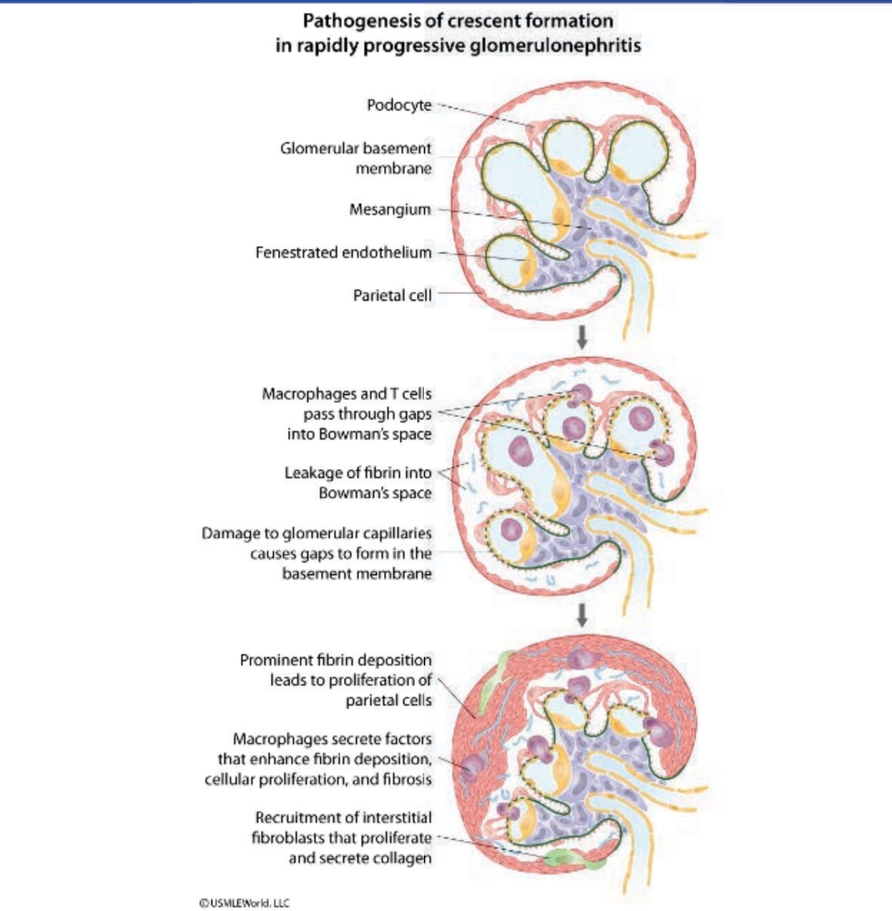
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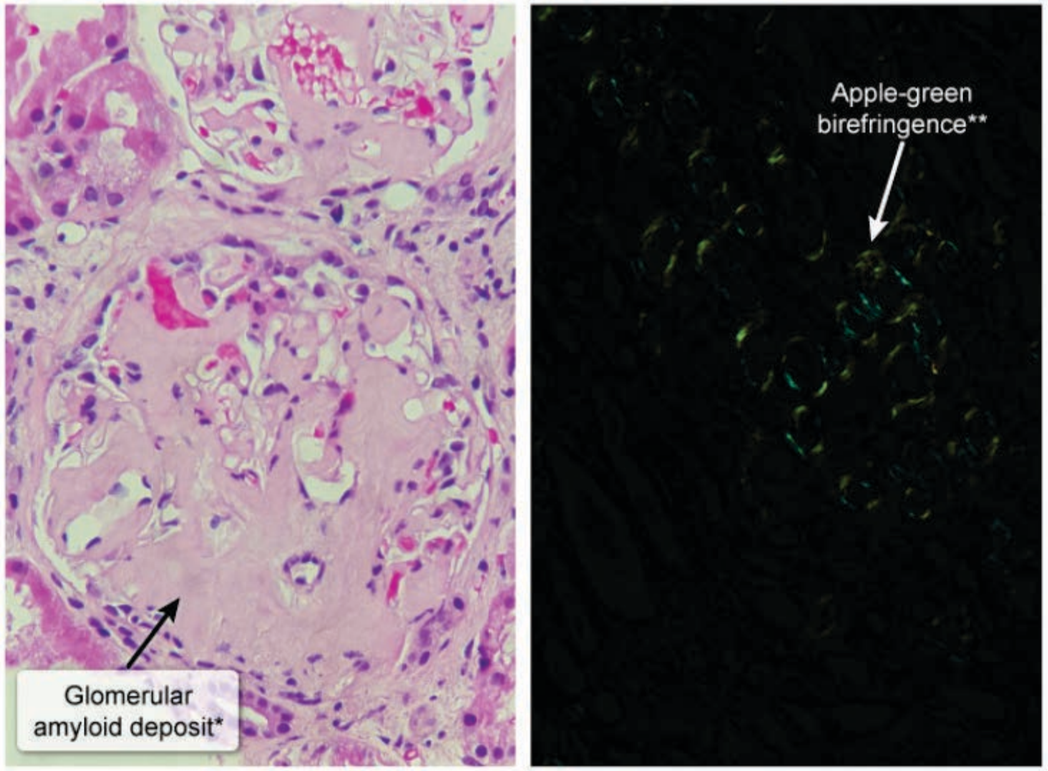
(Choice D) The clear cells seen in renal cell carcinoma (RCC) have a high lipid content, which is responsible for

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Correct
65% Answered correctly
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2023 Version

Exhibit Display

Amyloidosis of the kidney



*Pink, amorphous proteinaceous deposit
**Seen on Congo red staining under polarized light

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(Choice D) The clear cells seen in renal cell carcinoma (RCC) have a high lipid content, which is responsible for

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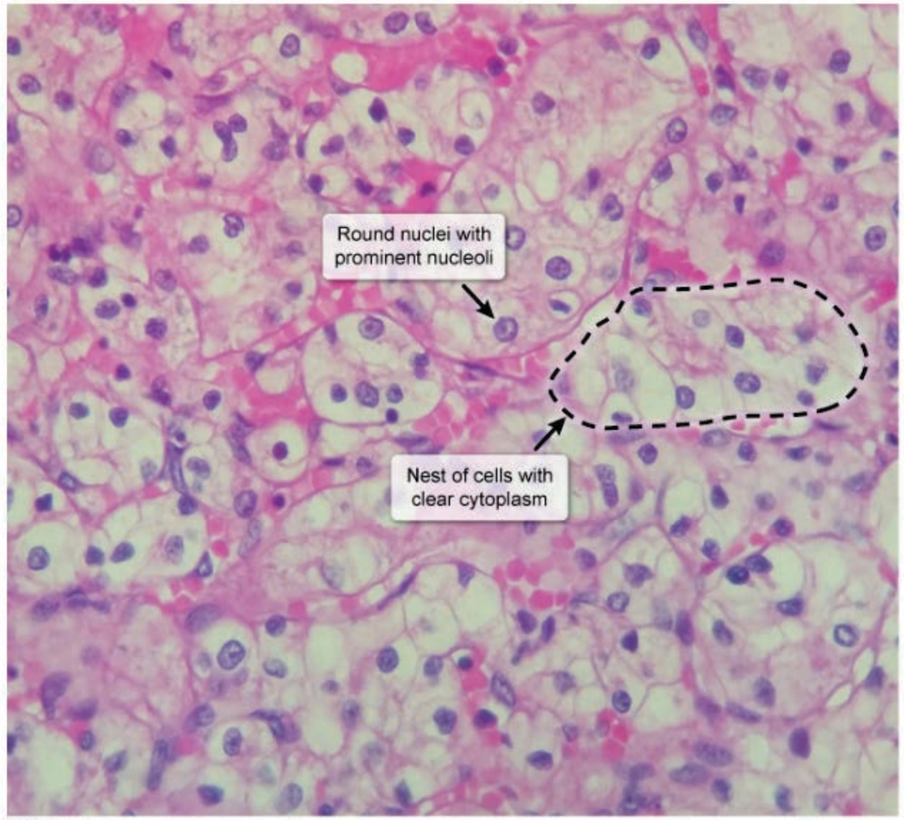
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of glomerular parietal cells, lymphocytes, and macrophages along with abundant fibrin deposition. Crescents

Exhibit Display

Renal clear cell carcinoma



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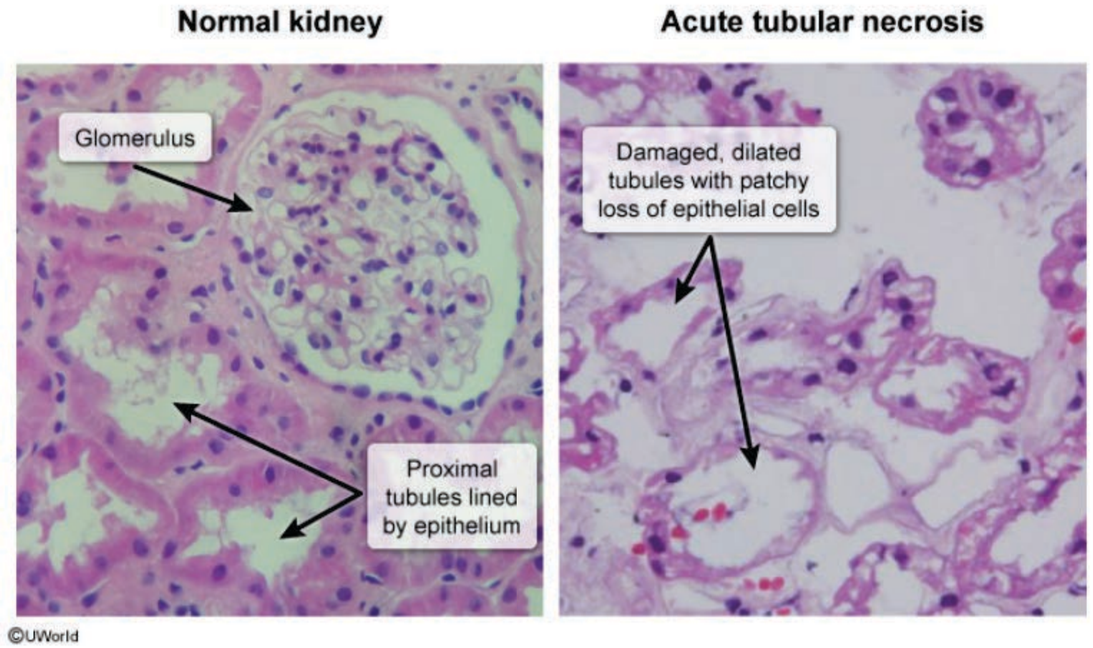
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of glomerular parietal cells, lymphocytes, and macrophages along with abundant fibrin deposition. Crescents

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A 28-year-old woman, gravida 1 para 0, at 12 weeks gestation comes to the office for follow-up. During the first trimester, the patient had mild nausea, which has now resolved, and the patient feels well. She has a history of epilepsy for which she is taking lamotrigine; her only other medication is a prenatal vitamin with folic acid. Vital signs and physical examination show no abnormalities. Fetal heart tones are normal. In addition to routine prenatal care, the patient's serum lamotrigine level is being closely monitored because the drug is eliminated primarily by the kidneys. Which of the following renal changes are expected in this patient during her pregnancy?

	Renal blood flow	Glomerular filtration rate	Serum creatinine level
○ A.	Decreased	Decreased	Increased
○ B.	Decreased	Unchanged	Decreased
○ C.	Increased	Decreased	Unchanged
○ D.	Increased	Increased	Decreased
○ E.	Unchanged	Increased	Increased

Submit

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A 28-year-old woman, gravida 1 para 0, at 12 weeks gestation comes to the office for follow-up. During the first trimester, the patient had mild nausea, which has now resolved, and the patient feels well. She has a history of epilepsy for which she is taking lamotrigine; her only other medication is a prenatal vitamin with folic acid. Vital signs and physical examination show no abnormalities. Fetal heart tones are normal. In addition to routine prenatal care, the patient's serum lamotrigine level is being closely monitored because the drug is eliminated primarily by the kidneys. Which of the following renal changes are expected in this patient during her pregnancy?

		Renal blood flow	Glomerular filtration rate	Serum creatinine level	
✗	A.	Decreased	Decreased	Increased	(16%)
	B.	Decreased	Unchanged	Decreased	(1%)
	C.	Increased	Decreased	Unchanged	(9%)
✓	D.	Increased	Increased	Decreased	(61%)
	E.	Unchanged	Increased	Increased	(10%)

Incorrect
Correct answer
D

61%
Answered correctly

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Time Spent

2023
Version

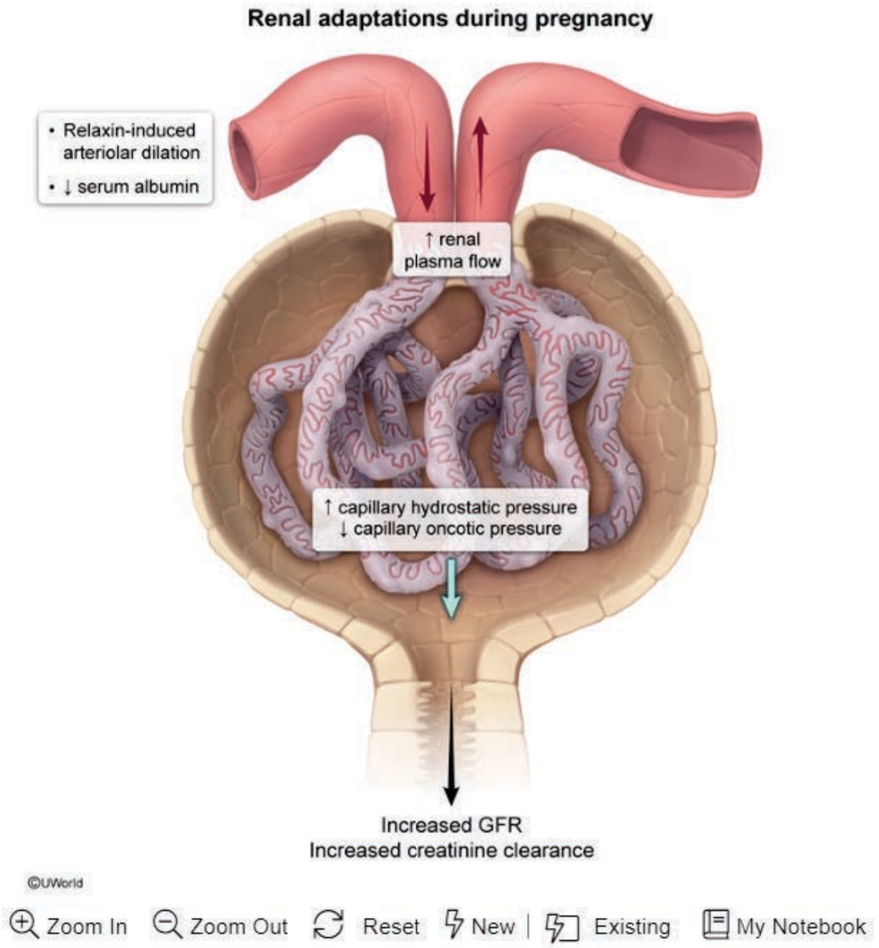
Explanation

Renal adaptations during pregnancy

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flow filtration rate level

Exhibit Display



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Pregnancy results in multiple maternal hemodynamic changes that affect renal physiology. Marked **volume expansion** occurs due to renin release from extrarenal sources (eg, ovaries, decidua) with upregulation of the renin-angiotensin-aldosterone system (RAAS). Despite the increased sodium and water retention and RAAS activity, pregnancy is marked by **widespread vasodilation** and increased arterial compliance, likely due to the release of relaxin and reduced sensitivity to angiotensin II and norepinephrine.

Increased blood volume and cardiac output result in the following alterations in renal hemodynamics:

- **Increased renal plasma flow (RPF)**, which peaks at 12 weeks gestation.
- **Increased glomerular filtration rate**, which is largely driven by the increased RPF. However, later in gestation, the dilutional reduction in serum albumin levels results in lower plasma oncotic pressure and further promotes filtration.

These alterations result in increased creatinine clearance, leading to **decreased serum creatinine levels**, typically by an average reduction of approximately 0.4 mg/dL. Therefore, serum creatinine levels considered normal in nonpregnant patients (eg, 1.0 mg/dL) represent significant renal dysfunction in this population. Furthermore, a small rise in creatinine in a pregnant woman reflects a marked reduction in renal function.

(Choices A, B, C, and E) These hemodynamic alterations would not occur in normal pregnancy and represent renal dysfunction in a pregnant patient.

Educational objective:
Pregnancy results in significant plasma expansion and widespread vasodilation, leading to increased renal plasma flow and glomerular filtration rates. Serum creatinine is reduced by approximately 0.4 mg/dL in this population; therefore, a rise in serum creatinine, even to levels that are normal in nonpregnant patients, represents significant renal dysfunction.

Physiology | Renal, Urinary Systems & Electrolytes | GFR

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The following vignette applies to the next 2 items. The items in the set must be answered in sequential order. Once you click Proceed to Next Item, you will not be able to add or change an answer.

A 54-year-old previously healthy man comes to the office due to several weeks of leg swelling. He has had no fever, chest pain, or dyspnea. The patient has a 40-pack-year smoking history but does not use alcohol or illicit drugs. He is afebrile and vital signs are within normal limits. On physical examination, there is symmetric pitting edema of the lower extremities bilaterally. The abdomen is soft and nondistended. A mobile left flank mass can be palpated. There are several vertically oriented tortuous veins on the lower abdominal wall.

Item 1 of 2

Which of the following structures is most likely obstructed in this patient?

- A. Femoral veins
- B. Iliac veins
- C. Inferior vena cava
- D. Portal vein
- E. Saphenous veins

Submit

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Item 2 of 2

Further evaluation of the patient reveals microscopic hematuria. Laboratory results are as follows:

Leukocytes	9,000/mm^3
Hemoglobin	19.2 g/dL
Platelets	230,000/mm^3

Which of the following is the most likely cause of this patient's hematologic findings?

- A. Arteriovenous malformation
- B. Excess erythropoietin production
- C. Extramedullary hematopoiesis
- D. Myeloproliferative disorder
- E. Reduced plasma volume

Submit

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The following vignette applies to the next 2 items. The items in the set must be answered in sequential order. Once you click Proceed to Next Item, you will not be able to add or change an answer.

A 54-year-old previously healthy man comes to the office due to several weeks of leg swelling. He has had no fever, chest pain, or dyspnea. The patient has a 40-pack-year smoking history but does not use alcohol or illicit drugs. He is afebrile and vital signs are within normal limits. On physical examination, there is symmetric pitting edema of the lower extremities bilaterally. The abdomen is soft and nondistended. A mobile left flank mass can be palpated. There are several vertically oriented tortuous veins on the lower abdominal wall.

Item 1 of 2

Which of the following structures is most likely obstructed in this patient?

- A. Femoral veins (3%)
- ✗ B. Iliac veins (17%)
- ✓ C. Inferior vena cava (37%)
- D. Portal vein (38%)
- E. Saphenous veins (2%)

Incorrect
Correct answer
C

37%
Answered correctly

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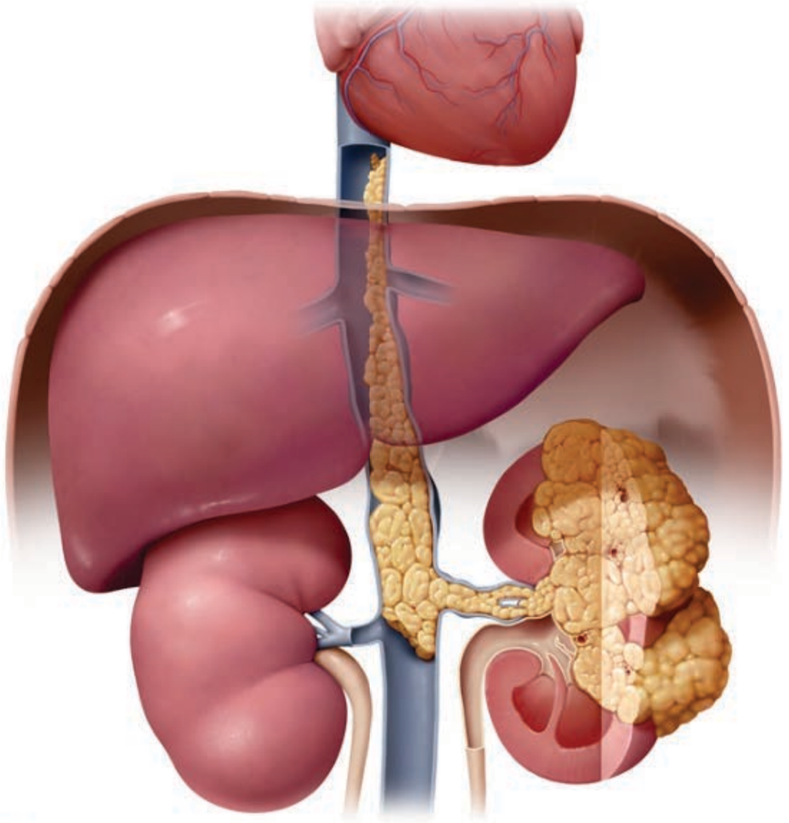
Explanation

Renal cell carcinoma & IVC obstruction

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Exhibit Display

Renal cell carcinoma & IVC obstruction



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This patient's symmetric bilateral lower extremity pitting edema and tortuous abdominal veins are concerning for an **inferior vena cava (IVC) obstruction**, which, in the setting of a left-sided flank mass, suggests **renal cell**

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This patient's symmetric bilateral lower extremity pitting edema and tortuous abdominal veins are concerning for an **inferior vena cava (IVC) obstruction**, which, in the setting of a left-sided flank mass, suggests **renal cell carcinoma** (RCC) with extension into the IVC. RCC accounts for >90% of all malignancies arising in the kidney and is highly associated with smoking. Patients with RCC classically have a triad of flank pain, palpable mass, and hematuria, although many remain asymptomatic until the disease is advanced.

RCC is a highly vascular tumor that **invades the renal vein** in up to 25% of cases. IVC obstruction can occur due to intraluminal extension and thrombus formation, rather than mass effect from the tumor itself. The obstruction can occur acutely or gradually over time. In chronic cases, collateral venous circulation may develop based on the site of the obstruction. Prominent abdominal wall **collateral veins**, as in this patient, suggest obstruction of the upper segment of the IVC.

(Choices A, B, and E) The femoral, iliac, and saphenous veins are too low in the legs to produce significant abdominal wall collateral veins if obstructed. Obstruction of these veins would be more likely to cause varices on the legs, thighs, and hips. In addition, unilateral (rather than bilateral) lower extremity edema would be expected.

(Choice D) Obstruction of the portal vein is most commonly associated with severe hepatic cirrhosis. Affected patients have shunting of blood through portocaval anastomoses, leading to hemorrhoids, esophageal varices, and caput medusae about the umbilicus. They may also have ascites.

Educational objective:
Renal cell carcinoma tends to invade the renal vein; inferior vena cava obstruction can occur by intraluminal extension of the tumor. Obstruction of the inferior vena cava produces symmetric bilateral lower extremity edema, often associated with prominent development of venous collaterals in the abdominal wall.

References

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Item 2 of 2

Further evaluation of the patient reveals microscopic hematuria. Laboratory results are as follows:

Leukocytes	9,000/mm^3
Hemoglobin	19.2 g/dL
Platelets	230,000/mm^3

Which of the following is the most likely cause of this patient's hematologic findings?

- A. Arteriovenous malformation (1%)
- ✓ B. Excess erythropoietin production (78%)
- C. Extramedullary hematopoiesis (5%)
- D. Myeloproliferative disorder (8%)
- E. Reduced plasma volume (5%)

Correct

78% Answered correctly

07 secs Time Spent

2023 Version

Explanation

This patient most likely has **renal cell carcinoma** with an elevated hemoglobin level suggestive of erythrocytosis. Renal cell carcinoma causes a variety of paraneoplastic syndromes. **Erythrocytosis** is an uncommon but classic finding and is the result of excessive erythropoietin production by the renal cell tumor. Hypercalcemia may also occur due to overproduction of parathyroid hormone–related peptide or from lytic bone metastases.

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Answered correctly
Time Spent
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Explanation

This patient most likely has **renal cell carcinoma** with an elevated hemoglobin level suggestive of erythrocytosis. Renal cell carcinoma causes a variety of paraneoplastic syndromes. **Erythrocytosis** is an uncommon but classic finding and is the result of excessive erythropoietin production by the renal cell tumor. Hypercalcemia may also occur due to overproduction of parathyroid hormone–related peptide or from lytic bone metastases.

(Choice A) Arteriovenous malformations have been associated with high-output cardiac failure, local bony hypertrophy, and local tissue compression and distortion. These lesions are typically congenital although they may not become clinically evident until puberty.

(Choice C) When intramedullary hematopoiesis is insufficient, blood cell formation can sometimes occur in extramedullary sites such as the liver, spleen, and thymus, resulting in enlargement of these organs. Extramedullary hematopoiesis typically occurs in the setting of myelofibrosis.

(Choice D) Myeloproliferative disorders such as polycythemia vera typically cause increases in all cell lines (leukocytosis and thrombocytosis would also be expected).

(Choice E) Reduced plasma volume can cause a pseudo-elevation in hemoglobin/hematocrit levels. However, hemoconcentration typically causes this pseudo-elevation in all cell lines. In addition, there is no other indication of a reduced plasma volume, and in this clinical setting, erythropoietin overproduction from a renal tumor is more likely.

Educational objective:
Renal cell carcinoma causes a variety of paraneoplastic syndromes including erythrocytosis (due to excessive erythropoietin production) and hypercalcemia (due to parathyroid hormone–related peptide).

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A 73-year-old man comes to the office due to blood in his urine. He has noted bright red blood at the end of micturition on several occasions but has had no urinary frequency or pain with urination. The patient has a history of hypertension and chronic bronchitis. He has smoked a pack of cigarettes daily for 30 years. Temperature is 37 C (98.6 F). Abdominal, external genital, and rectal examinations are unremarkable. Urinalysis shows hematuria. Urine cytology is positive for malignant cells. Cystoscopy is planned for visualization and biopsy of suspected urinary tract cancer. Which of the following features would be most suggestive of a poor prognosis?

- A. High-grade intraepithelial lesion
- B. Involvement of the muscularis propria layer
- C. Location at the anterior bladder wall
- D. Papillary morphology
- E. Tumor size >2 cm

Submit

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- A. High-grade intraepithelial lesion (12%)
- ✓ B. Involvement of the muscularis propria layer (73%)
- C. Location at the anterior bladder wall (3%)
- D. Papillary morphology (4%)
- E. Tumor size >2 cm (6%)

Correct

73%
Answered correctly

03 secs
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Explanation

This patient with a significant **smoking** history has developed painless gross **hematuria**, which raises suspicion for bladder cancer. **Urothelial (transitional cell) carcinomas** arising from the transitional epithelium lining the bladder (ie, urothelium) are the most common type of bladder cancer; squamous cell and adenocarcinomas may occur but are significantly less common. Urothelial cancer typically grows as an erythematous papillary, nodular, or sessile mass and is easily diagnosed on **cystoscopy**. Microscopy may show cells resembling normal bladder epithelium but with irregular architecture, pleomorphism, hyperchromatic nuclei, and atypical mitoses

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Explanation

This patient with a significant **smoking** history has developed painless gross **hematuria**, which raises suspicion for bladder cancer. **Urothelial (transitional cell) carcinomas** arising from the transitional epithelium lining the bladder (ie, urothelium) are the most common type of bladder cancer; squamous cell and adenocarcinomas may occur but are significantly less common. Urothelial cancer typically grows as an erythematous papillary, nodular, or sessile mass and is easily diagnosed on **cystoscopy**. Microscopy may show cells resembling normal bladder epithelium but with irregular architecture, pleomorphism, hyperchromatic nuclei, and atypical mitoses.

Tumor stage is the most important factor for determining prognosis in urothelial carcinoma and is based on the **depth of invasion** into the bladder wall and the degree of spread to other tissues. Tumor penetration through the lamina propria **into the muscularis propria** layer (indicating stage T2 or higher in the Tumor, Node, Metastasis [TNM] system) carries an **unfavorable prognosis**.

(Choice A) Tumor grade, or the degree of cellular abnormality, also influences prognosis but to a lesser extent than staging. High-grade intraepithelial lesions (eg, urothelial carcinoma in situ), despite their high degree of cellular abnormality, have a relatively favorable prognosis as they have not yet invaded the basement membrane.

(Choice C) Urothelial tumors at the bladder neck may have an elevated risk of recurrence, but, in general, tumor location within the bladder has only a minor effect on prognosis.

(Choice D) Tumors with papillary morphology are more likely to extend into the bladder lumen rather than penetrate into the bladder wall. However, these tumors can become invasive, and papillary morphology itself does not directly influence prognosis.

(Choice E) Larger tumors are associated with worse prognosis; however, depth of tumor invasion is a much more important prognostic factor than tumor size.

Educational objective:
Urothelial (transitional cell) carcinoma is the most common type of bladder cancer. Tumor stage is the most

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bladder cancer. **Urothelial (transitional cell) carcinomas** arising from the transitional epithelium lining the bladder (ie, urothelium) are the most common type of bladder cancer; squamous cell and adenocarcinomas may occur but are significantly less common. Urothelial cancer typically grows as an erythematous papillary, nodular, or sessile mass and is easily diagnosed on **cystoscopy**. Microscopy may show cells resembling normal bladder epithelium but with irregular architecture, pleomorphism, hyperchromatic nuclei, and atypical mitoses.

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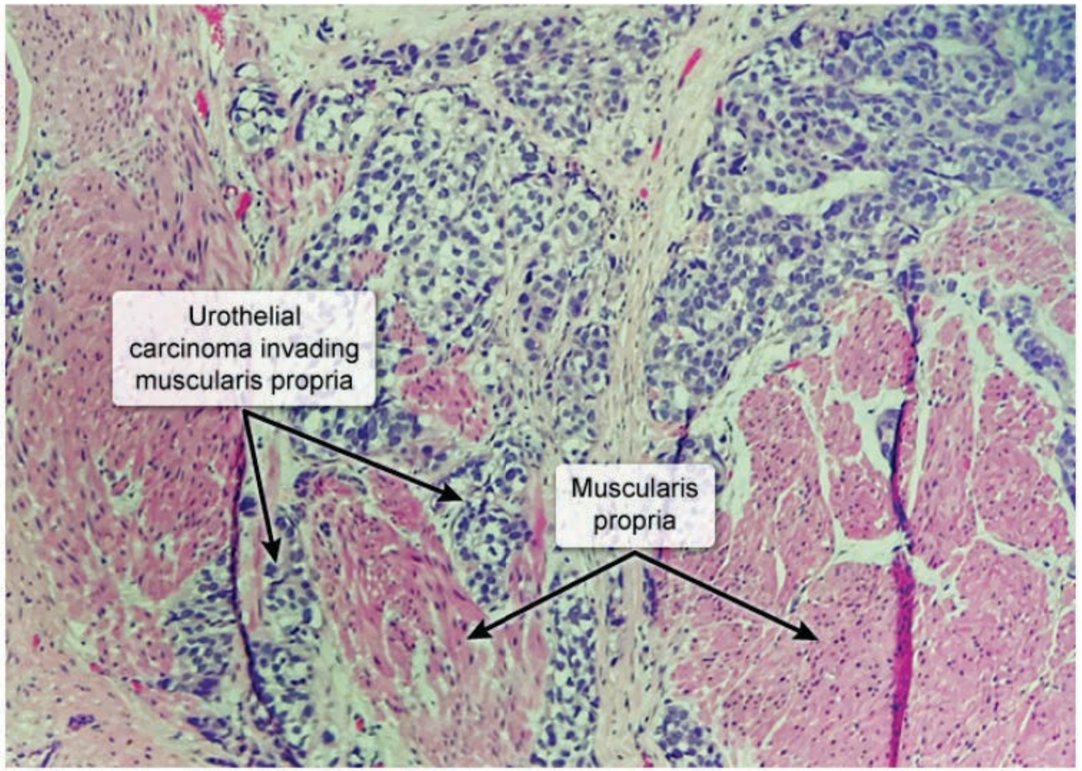
Educational objective:
Urothelial (transitional cell) carcinoma is the most common type of bladder cancer. Tumor stage is the most important factor for determining prognosis and is based on the depth of invasion into the bladder wall and the degree of regional (eg, lymph nodes) and metastatic spread. Tumor invasion into the muscularis propria layer of the bladder wall carries an unfavorable prognosis.

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Explanation

Exhibit Display

Invasive urothelial carcinoma of the bladder



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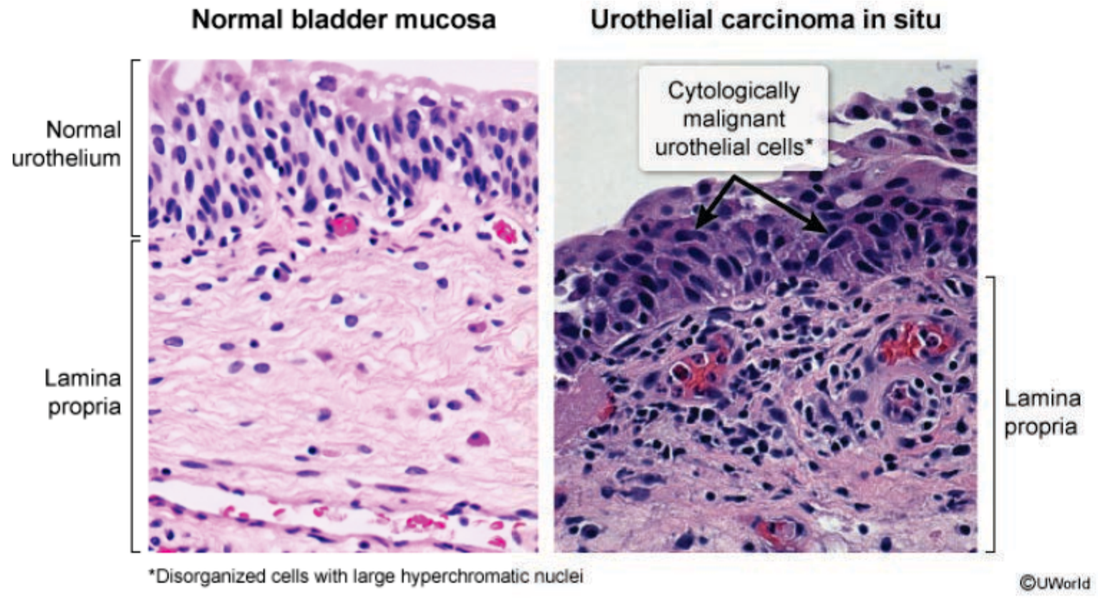
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Urothelial (transitional cell) carcinoma is the most common type of bladder cancer. Tumor stage is the most

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Explanation

Exhibit Display



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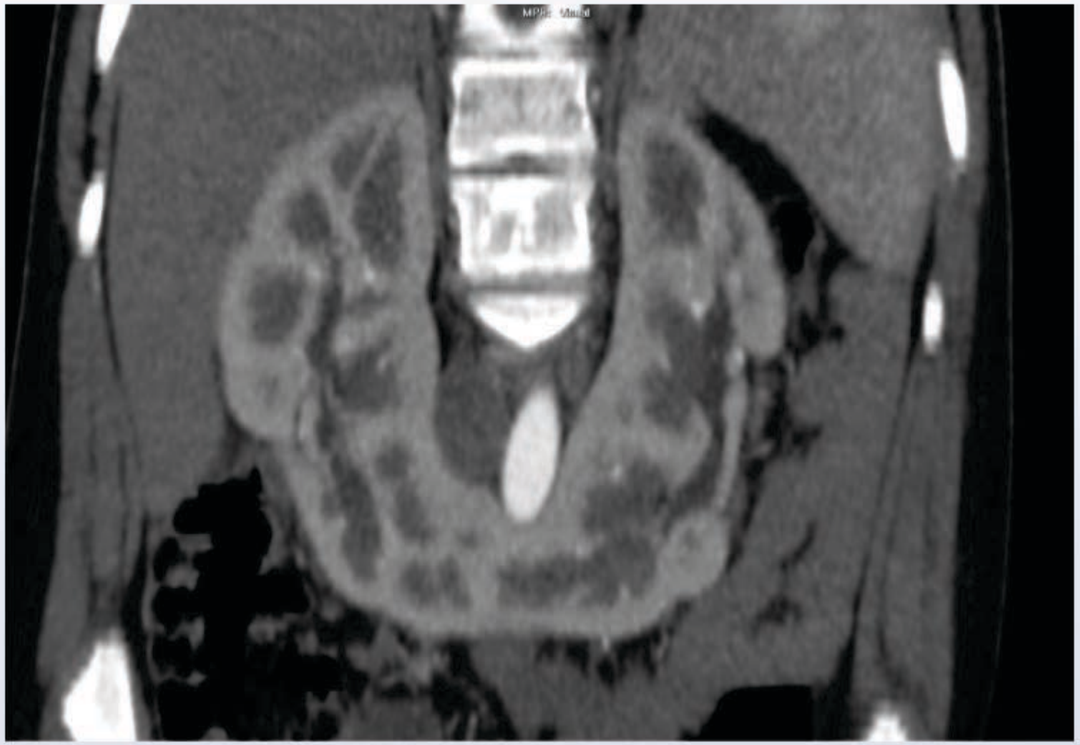
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Urothelial (transitional cell) carcinoma is the most common type of bladder cancer. Tumor stage is the most

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A 30-year-old woman comes to the clinic due to recurrent urinary tract infections. She also has a history of nephrolithiasis. Vital signs are normal, and examination is unremarkable. CT scan of the abdomen is shown below.



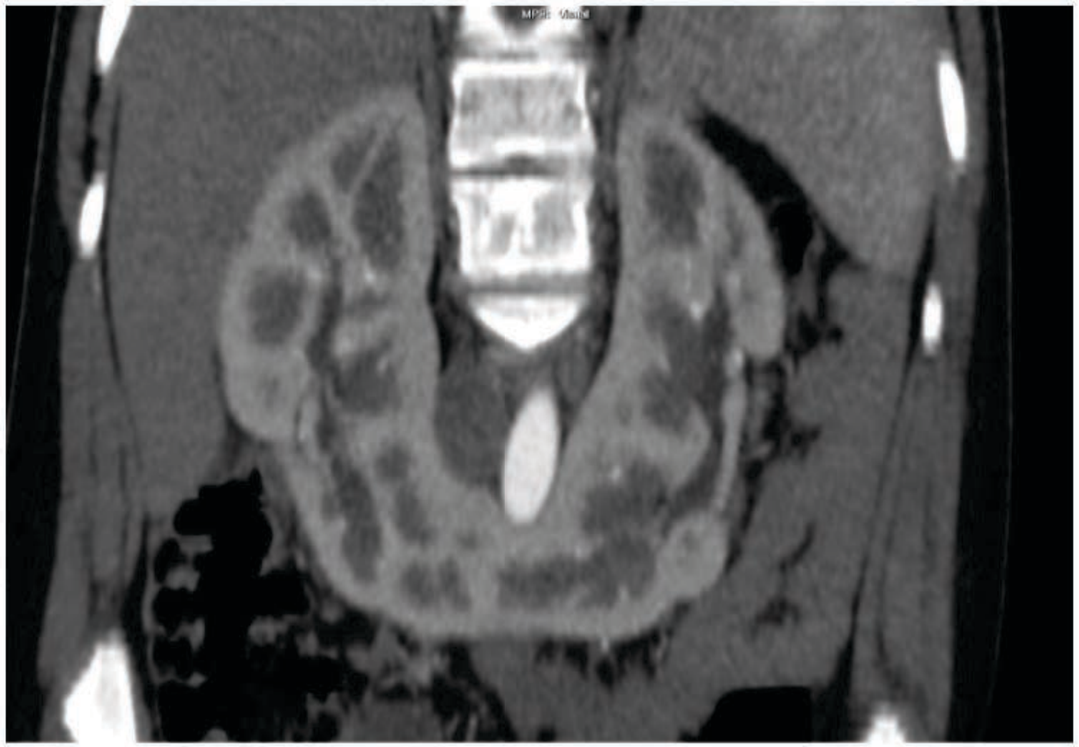
Fusion of which of the following embryologic structures most likely explains this patient's CT scan findings?

- A. Mesonephric duct
- B. Mesonephros
- C. Metanephros

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A 30-year-old woman comes to the clinic due to recurrent urinary tract infections. She also has a history of nephrolithiasis. Her kidneys are shown below.

Exhibit Display

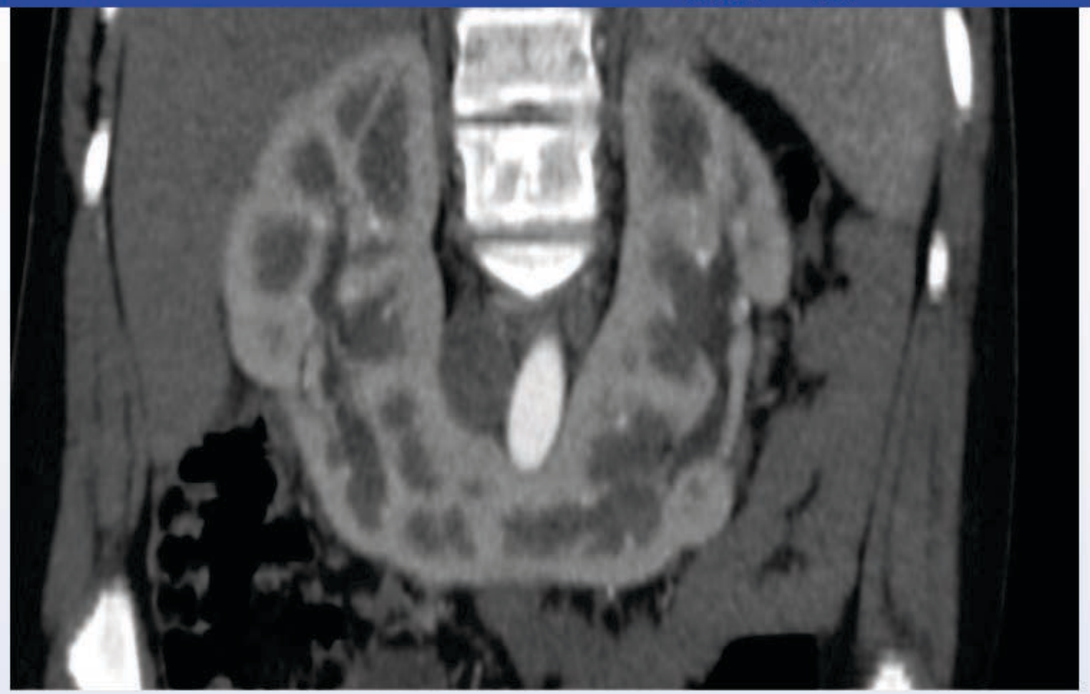


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Fusion of the kidneys is most commonly seen in which of the following?

C. Metanephros

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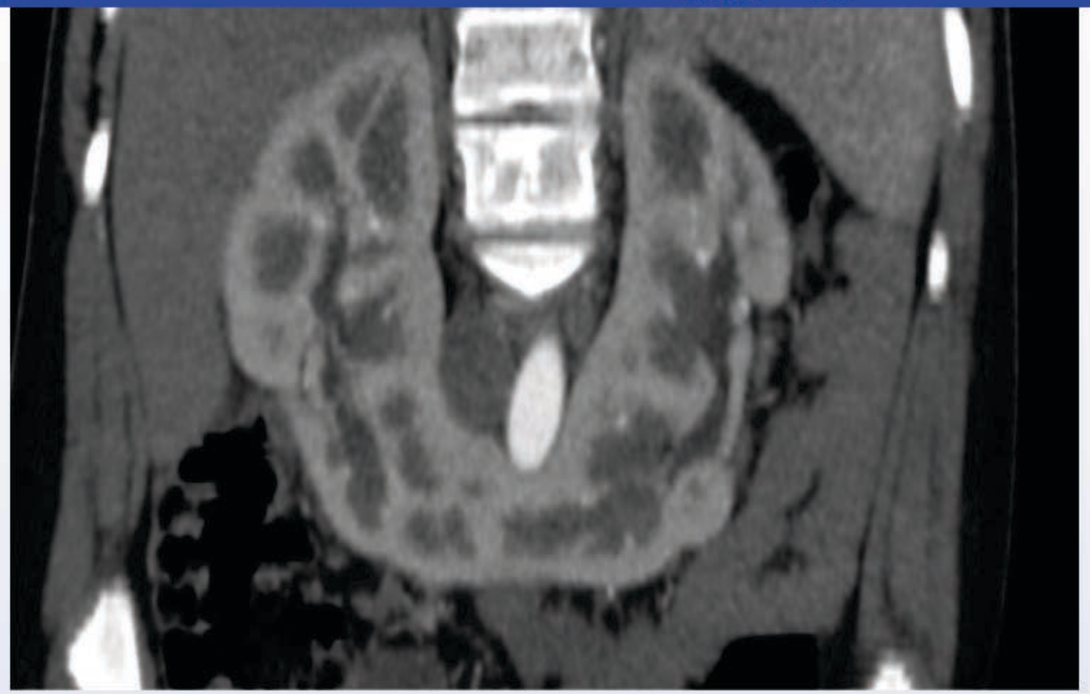


Fusion of which of the following embryologic structures most likely explains this patient's CT scan findings?

- A. Mesonephric duct
- B. Mesonephros
- C. Metanephros
- D. Pronephros
- E. Urogenital ridge

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Fusion of which of the following embryologic structures most likely explains this patient's CT scan findings?

- A. Mesonephric duct (13%)
- ✗ B. Mesonephros (22%)
- ✓ C. Metanephros (56%)
- D. Pronephros (2%)
- E. Urogenital ridge (5%)

Incorrect
Correct answer
C

56%
Answered correctly

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Incorrect
Correct answer

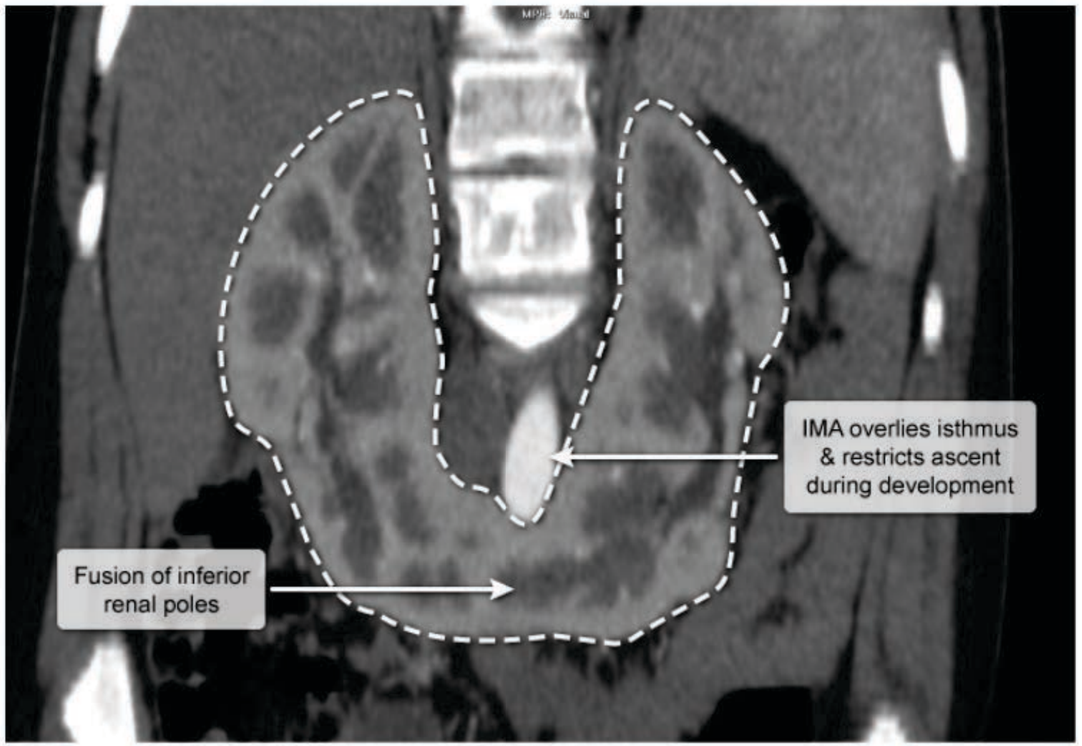
56%
Answered correctly

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Exhibit Display

Horseshoe kidney



IMA = inferior mesenteric artery.

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This
anomaly caused by fusion of the **metanephros** in utero.

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IMA = inferior mesenteric artery.

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This patient's CT scan shows fusion of the right and left renal parenchyma, or **horseshoe kidney**, a congenital anomaly caused by fusion of the **metanephros** in utero.

The metanephros is an embryologic structure that comprises the metanephric blastema, which gives rise to the renal parenchyma, and the ureteric bud, which gives rise to the renal collecting system and ureters. Abnormal migration of the right and left metanephric blastema can lead to **fusion** of this developing renal parenchyma **along the inferior poles**, forming a U or horseshoe shape. The fused kidneys begin their physiologic ascent from the pelvis into the abdomen until the isthmus (central fused portion) is physically restricted by the overlying inferior mesenteric artery at its origin from the aorta. As a result, compared to normal, horseshoe kidneys lie lower in the abdomen. The isthmus also displaces the renal pelvises superiorly, often causing the ureters to insert abnormally high and pass over the anterior portions of the kidneys or the isthmus.

Although horseshoe kidney is often an incidental or asymptomatic finding, patients are prone to intermittent ureteropelvic junction obstruction and urinary stasis due to the **abnormal orientation** of the kidneys and location of ureteral insertion. These consequences increase the risk for **nephrolithiasis** as well as retrograde urine flow (ie, reflux) and, therefore, **recurrent urinary tract infections**.

(Choices A, B, and D) The pronephros is a rudimentary nephric system that degenerates in early gestation. Similarly, much of the rudimentary mesonephros degenerates, although a portion (the mesonephric duct) persists as the ureteric bud. This patient has horseshoe kidney, a congenital defect involving the renal parenchyma, which is derived only from the metanephric blastema, a component of the metanephros.

(Choice E) Although the nephric systems (including pronephros, mesonephros, and metanephros) are all derived from the urogenital ridge, this structure also gives rise to the gonads, reproductive tract, and adrenal cortex in addition to the kidney. Horseshoe kidney is due to fusion of the metanephros alone.

Educational objective:
Horseshoe kidney is a congenital anomaly in which fusion of the metanephros (specifically, metanephric blastema)

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The metanephros is an embryologic structure that comprises the metanephric blastema, which gives rise to the renal parenchyma, and the ureteric bud, which gives rise to the renal collecting system and ureters. Abnormal migration of the right and left metanephric blastema can lead to **fusion** of this developing renal parenchyma **along the inferior poles**, forming a U or horseshoe shape. The fused kidneys begin their physiologic ascent from the pelvis into the abdomen until the isthmus (central fused portion) is physically restricted by the overlying inferior mesenteric artery at its origin from the aorta. As a result, compared to normal, horseshoe kidneys lie lower in the abdomen. The isthmus also displaces the renal pelvises superiorly, often causing the ureters to insert abnormally high and pass over the anterior portions of the kidneys or the isthmus.

Although horseshoe kidney is often an incidental or asymptomatic finding, patients are prone to intermittent ureteropelvic junction obstruction and urinary stasis due to the **abnormal orientation** of the kidneys and location of ureteral insertion. These consequences increase the risk for **nephrolithiasis** as well as retrograde urine flow (ie, reflux) and, therefore, **recurrent urinary tract infections**.

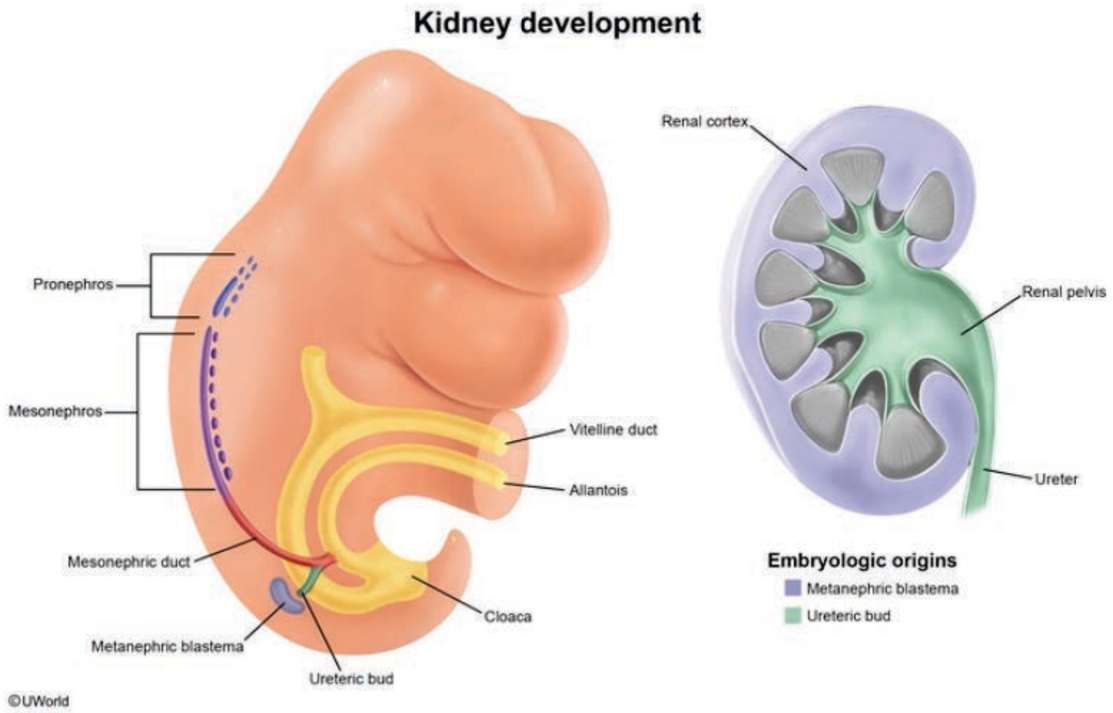
(Choices A, B, and D) The pronephros is a rudimentary nephric system that degenerates in early gestation. Similarly, much of the rudimentary mesonephros degenerates, although a portion (the mesonephric duct) persists as the ureteric bud. This patient has horseshoe kidney, a congenital defect involving the renal parenchyma, which is derived only from the metanephric blastema, a component of the metanephros.

(Choice E) Although the nephric systems (including pronephros, mesonephros, and metanephros) are all derived from the urogenital ridge, this structure also gives rise to the gonads, reproductive tract, and adrenal cortex in addition to the kidney. Horseshoe kidney is due to fusion of the metanephros alone.

Educational objective:
Horseshoe kidney is a congenital anomaly in which fusion of the metanephros (specifically, metanephric blastema) results in fused renal parenchyma along the inferior poles. Most patients are asymptomatic, but some may develop recurrent urinary tract infections or nephrolithiasis due to abnormal urine flow through the malpositioned kidney and ureters.

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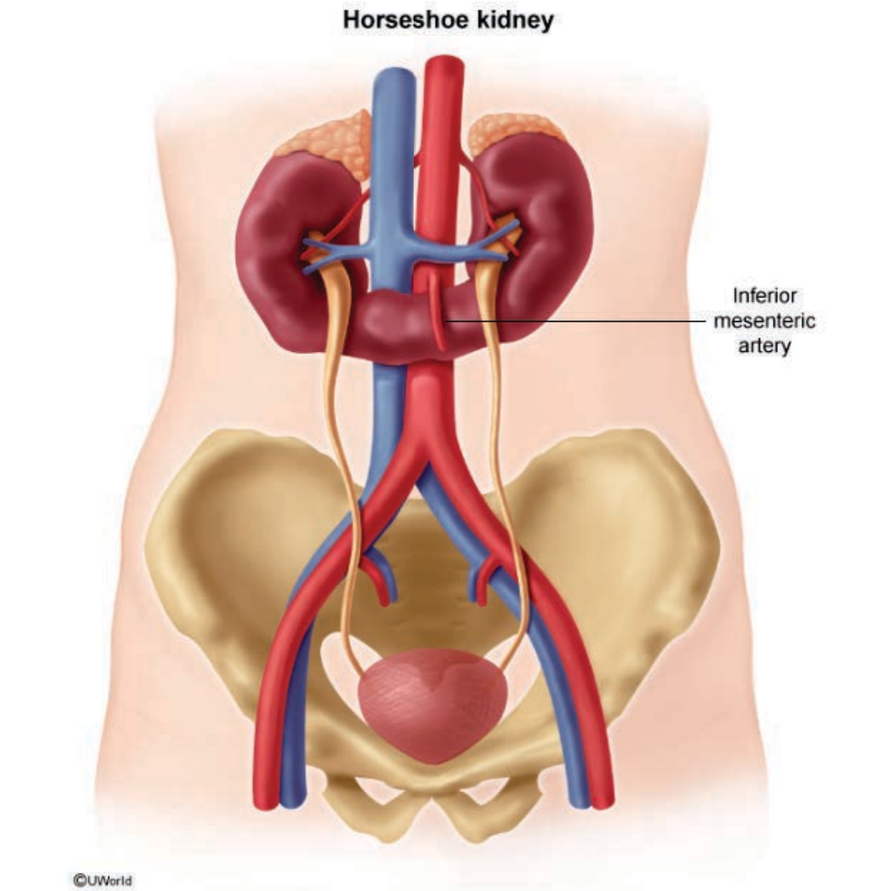
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(Choices A, B, and D) The pronephros is a rudimentary nephric system that degenerates in early gestation.

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An apparently healthy 6-year-old boy is enrolled in a research study designed to assess the absorptive capacity of the small intestine. As part of the investigation, he is administered an oral solution containing free amino acids and amino acid derivatives. Blood samples are then obtained at 15-minute intervals for the next 2 hours. The patient is found to have significantly decreased intestinal absorption of lysine, arginine, ornithine, and cystine as compared to the other study participants. If the condition is left untreated, which of the following complications is this patient at greatest risk of developing?

- A. Aortic dissection
- B. Fat-soluble vitamin deficiency
- C. Intellectual disability
- D. Kidney stones
- E. Rickets

Submit

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- ✗ A. Aortic dissection (3%)
- B. Fat-soluble vitamin deficiency (6%)
- C. Intellectual disability (27%)
- ✓ D. Kidney stones (58%)
- E. Rickets (3%)

Incorrect
Correct answer
D

58%
Answered correctly

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Explanation

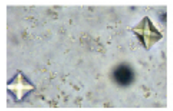
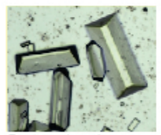
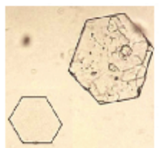
Nephrolithiasis				
Content	**Frequency**	**Radiograph opacity**	**pH**	**Microscopic appearance**
				

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Nephrolithiasis

Content	Frequency	Radiograph opacity	pH	Microscopic appearance
Calcium oxalate	70%-80%	↑↑	--	 • Octahedron (square with an "X" in the center)
Calcium phosphate			>7.0	• Elongated, wedge-shaped • Forms rosettes
Magnesium ammonium phosphate (struvite or triple phosphate)	15%	↑	>7.0	 • Rectangular prism ("coffin lids")
Uric acid	5%	--	<7.0	 • Yellow or red-brown, diamond or rhombus
Cystine	1%	↑	<7.0	 • Flat, yellow, **hexagonal**

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Cystine (a cysteine homodimer forming disulfide bonds) and the dibasic amino acids **o**rnithine, **l**ysine, and **a**rginine (**cola**) share a common transporter in the intestinal lumen and kidneys. In patients with **cystinuria**, this transporter is defective, resulting in impaired intestinal absorption and renal reabsorption.

- In the intestine, this impairment causes absent (or diminished) intestinal absorption of ornithine, lysine, and arginine. However, patients do not develop amino acid deficiencies because these amino acids are absorbed in sufficient quantities as **oligopeptides**.
- In the kidneys, impaired tubular reabsorption leads to a high urinary cystine concentration, resulting in the formation of **cystine kidney stones**. The amino acids ornithine, lysine, and arginine are relatively soluble in urine and do not result in the formation of kidney stones.

Risk factors for cystine precipitation include **low urine pH** (pH <7), the presence of a preexisting crystal nidus, and **urine supersaturation**.

(Choice A) Aortic dissection is a well-known complication of connective tissue disorders (eg, Marfan). Although amino acid deficiencies (eg, lysine) could cause weak connective tissue (eg, decreased collagen crosslinking), patients with cystinuria are not deficient in amino acids due to adequate absorption (via oligopeptides).

(Choice B) Fat-soluble vitamin deficiencies are typically seen in conditions that cause exocrine pancreas dysfunction (eg, cystic fibrosis) or reduced bile acid secretion. However, cystinuria is due to a defective amino acid transporter; absorption of fat and fat-soluble vitamins is not affected.

(Choice C) Intellectual disability occurs in several inborn errors of amino acid metabolism, including homocystinuria, which results from impaired conversion of methionine to cysteine. However, intellectual disability is not seen in cystinuria.

(Choice E) Rickets is a failure of osteoid calcification that occurs in children. Cystinuria does not affect bone calcification. In contrast, cystinosis, a lysosomal storage disease associated with renal tubular acidosis and impaired phosphate reabsorption, frequently causes vitamin D-resistant rickets due to hypophosphatemia.

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Educational objective:
Cystinuria is an autosomal recessive disorder caused by defective transportation of cystine, ornithine, arginine, and lysine across the intestinal and renal tubular epithelium. Recurrent nephrolithiasis is the only clinical manifestation. Urinalysis shows pathognomonic hexagonal cystine crystals.

Pathophysiology Renal, Urinary Systems & Electrolytes Cystinuria

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Researchers working at a national foundation for prematurity and birth defects are investigating the physiologic processes that occur during embryonic kidney development. Their research focuses on the inductive signals exchanged between the metanephric diverticulum and metanephric blastema that drive their differentiation into tissues forming the mature kidney. The researchers develop a method to reproduce the inductive signal that normally comes from the metanephric diverticulum. After applying this inductive signal to the metanephric blastema, which of the following adult derivatives will most likely develop?

- A. Collecting ducts
- B. Distal convoluted tubules
- C. Major calyces
- D. Minor calyces
- E. Renal pelvis

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- A. Collecting ducts (18%)
- ✓ B. Distal convoluted tubules (39%)
- C. Major calyces (9%)
- D. Minor calyces (2%)
- E. Renal pelvis (29%)

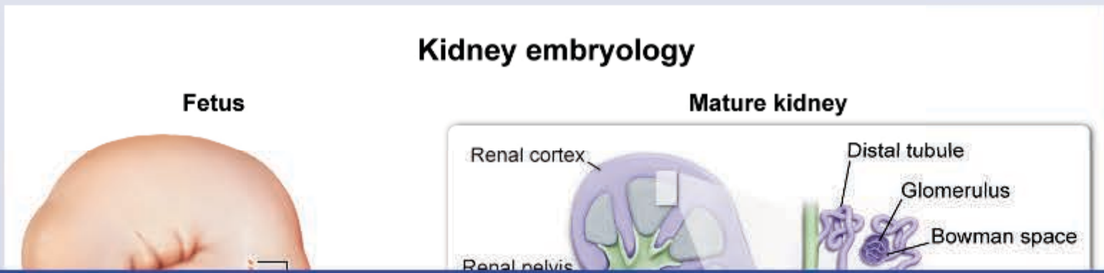
Correct

39% Answered correctly

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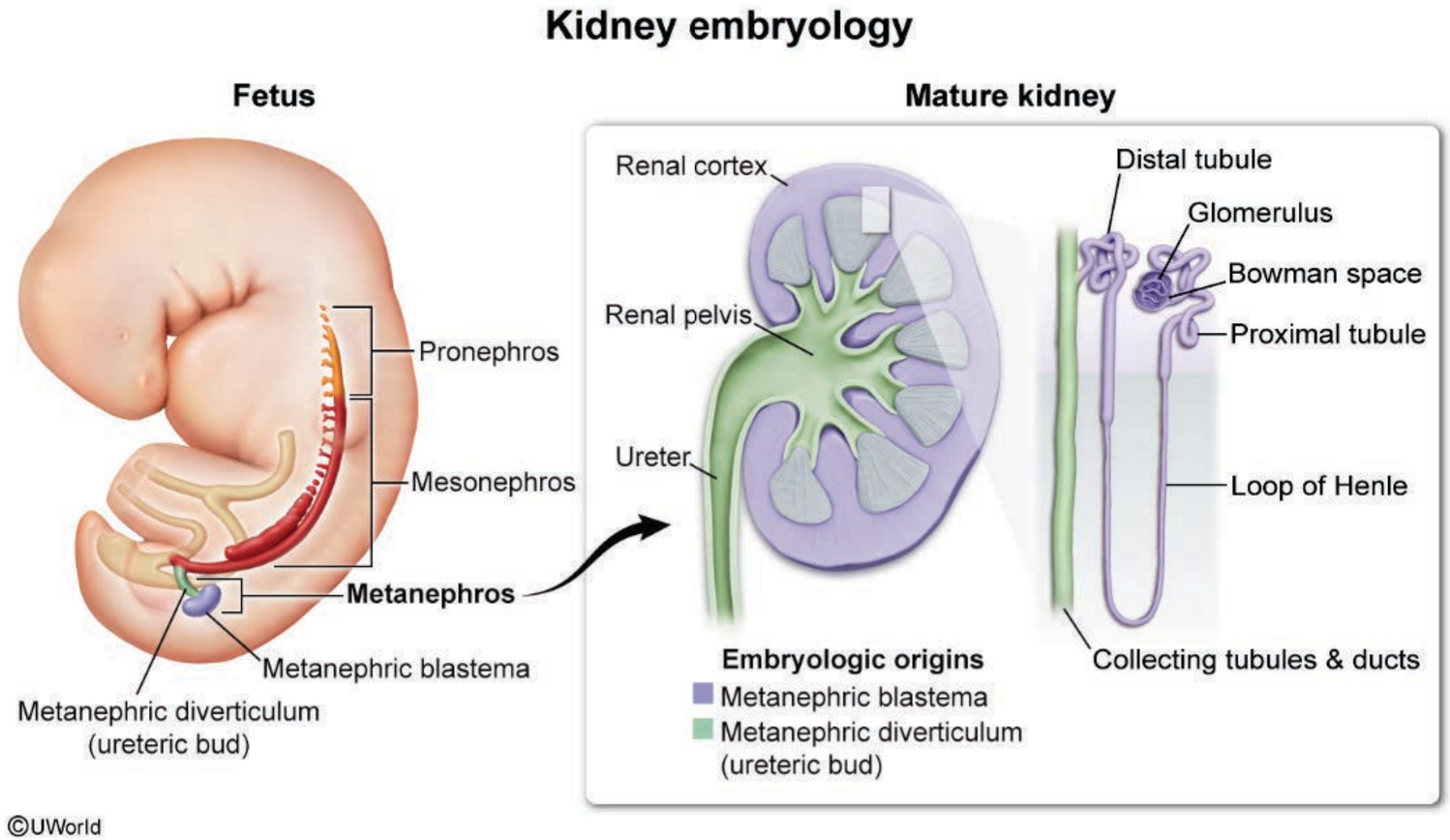
Explanation



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E. Renal pelvis (29%)

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ridge
mesonephros, and metanephros.

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Embryonic kidney development begins with the formation of the nephrogenic cord (derived from the urogenital ridge, or intermediate mesoderm). The cord sequentially forms 3 sets of nephric systems: pronephros, mesonephros, and metanephros.

The rudimentary pronephros forms first and later completely regresses. The **mesonephros** forms next from the midportion of the nephrogenic cord; in females, it regresses, whereas in males it persists as the **wolffian ducts**, forming the ductus deferens and epididymis.

The **metanephros** forms last from the caudal end of the nephrogenic cord and persists as the **mature upper urinary tract**. Development of the metanephros begins with formation of the metanephric diverticulum (ureteric bud), which penetrates the sacral intermediate mesoderm to induce the formation of the metanephric blastema. The reciprocal exchange of **inductive signals** between the ureteric bud and metanephric blastema drives their differentiation into the structures that form the upper urinary tract.

- **Metanephric blastema**: This structure gives rise to the glomeruli, Bowman space, proximal tubules, loop of Henle, and **distal convoluted tubules**.
- Metanephric diverticulum (ureteric bud): This structure gives rise to the collecting system of the kidney, including the collecting tubules and ducts, major and minor calyces, renal pelvis, and ureters **(Choices A, C, D, and E)**.

Educational objective:
The mature upper urinary tract is derived from the metanephros, which comprises the metanephric blastema and metanephric diverticulum (ureteric bud). The metanephric blastema gives rise to the glomeruli, Bowman space, proximal tubules, loop of Henle, and distal convoluted tubules. The ureteric bud becomes the collecting system of the kidney (eg, collecting tubules and ducts, major and minor calyces, renal pelvis, ureters).

References

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A 44-year-old woman comes to the emergency department due to acute-onset, severe, right lower quadrant abdominal pain, nausea, vomiting, and hematuria over the last 4 hours. She had a similar episode of acute pain a year ago, but it resolved in a few hours and she did not seek medical intervention. The patient has no other medical conditions and takes no medication. She smokes a pack of cigarettes daily. She is sexually active and has never been pregnant. Temperature is 36.9 C (98.4 F), blood pressure is 140/90 mm Hg, and pulse is 102/min. There is mild tenderness to deep palpation in the right lower quadrant. Laboratory results are as follows:

Serum chemistry	
Urea nitrogen	15 mg/dL
Creatinine	1.0 mg/dL
Glucose	90 mg/dL
Calcium	11 mg/dL
Phosphorus	2.5 mg/dL

Which of the following is the most likely cause of this patient's current condition?

- A. Appendicitis
- B. Diverticulitis
- C. Glomerulonephritis
- D. Ovarian torsion
- E. Renal cell carcinoma
- F. Renal infarction
- G. Ureterolithiasis

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Serum chemistry	
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Creatinine	1.0 mg/dL
Glucose	90 mg/dL
Calcium	11 mg/dL
Phosphorus	2.5 mg/dL

Which of the following is the most likely cause of this patient's current condition?

- A. Appendicitis (3%)
- B. Diverticulitis (1%)
- C. Glomerulonephritis (1%)
- D. Ovarian torsion (5%)
- E. Renal cell carcinoma (9%)
- F. Renal infarction (3%)
- ✓ G. Ureterolithiasis (74%)

Correct

74% Answered correctly

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Explanation

Risk & prevention of kidney stones		
Stone type	**Risk factors**	**Prevention**
Calcium stones (oxalate, phosphate)	• Hypercalciuria (eg, hyperparathyroidism) • Hyperoxaluria (eg, malabsorption, low-calcium diet) • Hypocitraturia (eg, distal RTA) • Diet: ↑ sodium, ↑ protein, ↑ oxalate, ↓ calcium	• Reduce sodium, animal protein, oxalate intake • Increase potassium intake; moderate calcium intake • Thiazide diuretics
Uric acid	• Gout • Myeloproliferative disorders	• Urine alkalinization • Allopurinol
Magnesium ammonium phosphate (struvite)	• Recurrent upper urinary infection (eg, *Klebsiella*, *Proteus*)	• Stone removal • Suppressive antibiotics
All types	• Dehydration	• Increase fluid intake
RTA = renal tubular acidosis.		

This patient has recurrent **abdominal pain**, vomiting, and **hematuria**. In conjunction with hypercalcemia and hypophosphatemia, this presentation suggests **ureterolithiasis** due to hyperparathyroidism. Most kidney stones are made up of calcium salts and are idiopathic, but conditions that increase calcium excretion increase the risk of stone formation. Primary hyperparathyroidism leads to increased bone resorption, decreased urinary phosphate reabsorption, and increased 1,25-dihydroxyvitamin D formation, all of which result in **hypercalcemia** and **hypophosphatemia**. Despite the increased fractional reabsorption of calcium induced by PTH, net urinary calcium excretion is elevated due to the increased filtered calcium load, raising the risk for stone formation.

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This patient has recurrent **abdominal pain**, vomiting, and **hematuria**. In conjunction with hypercalcemia and hypophosphatemia, this presentation suggests **ureterolithiasis** due to hyperparathyroidism. Most kidney stones are made up of calcium salts and are idiopathic, but conditions that increase calcium excretion increase the risk of stone formation. Primary hyperparathyroidism leads to increased bone resorption, decreased urinary phosphate reabsorption, and increased 1,25-dihydroxyvitamin D formation, all of which result in **hypercalcemia** and **hypophosphatemia**. Despite the increased fractional reabsorption of calcium induced by PTH, net urinary **calcium excretion is elevated** due to the increased filtered calcium load, raising the risk for stone formation.

Pain from ureterolithiasis, which occurs when the stone obstructs renal drainage, typically waxes and wanes. Obstruction at the ureteropelvic junction normally presents with flank or upper abdominal pain, whereas an obstructing stone at the ureterovesical junction usually presents with lower abdominal or groin pain. Other common symptoms include hematuria, nausea, and vomiting.

(Choices A and B) Appendicitis presents with acute periumbilical or right lower quadrant pain and tenderness, but it would not usually cause recurrent symptoms. Acute diverticulitis can cause recurrent lower abdominal symptoms but is much more common on the left and typically occurs in older (age >60) patients. Neither of these conditions are associated with hematuria or hypercalcemia.

(Choice C) Glomerulonephritis is a category of kidney disorders characterized by hematuria, typically with red cell casts. Common associated features include hypertension, oliguria, and acute renal failure. Patients with various nephritic syndromes may have moderate flank pain, but acute, severe lower abdominal pain is not consistent with glomerulonephritis.

(Choice D) Ovarian torsion can present with acute, severe lower abdominal or pelvic pain. It can be recurrent but would not cause hematuria.

(Choice E) Renal cell cancer can cause hematuria and hypercalcemia; however, pain (if present) typically presents in the flank rather than the lower abdomen.

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Obstruction at the ureteropelvic junction normally presents with flank or upper abdominal pain, whereas an obstructing stone at the ureterovesical junction usually presents with lower abdominal or groin pain. Other common symptoms include hematuria, nausea, and vomiting.

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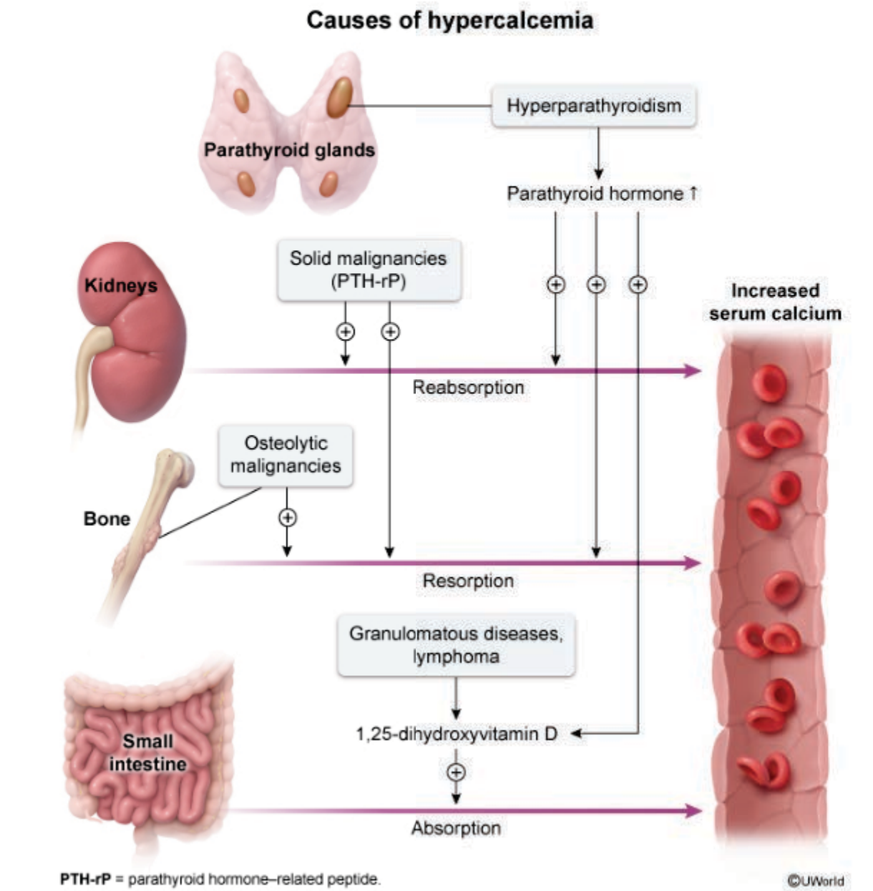
(Choice F) Renal infarction typically occurs due to acute obstruction of the renal arteries (eg, cardiac thromboembolism, aortic dissection). Patients often develop abdominal pain and hematuria but also typically have fever and marked hypertension (due to renin release). In addition, renal infarction is not associated with hypercalcemia or hypophosphatemia.

Educational objective:
Most kidney stones are made of calcium salts and are idiopathic, but conditions that increase renal calcium excretion can increase the risk of stones. Hyperparathyroidism is a common cause of recurrent kidney stones and is typically associated with mild hypercalcemia and hypophosphatemia.

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Uric acid	• Gout • Myeloproliferative disorders	• Urine alkalinization • Allopurinol

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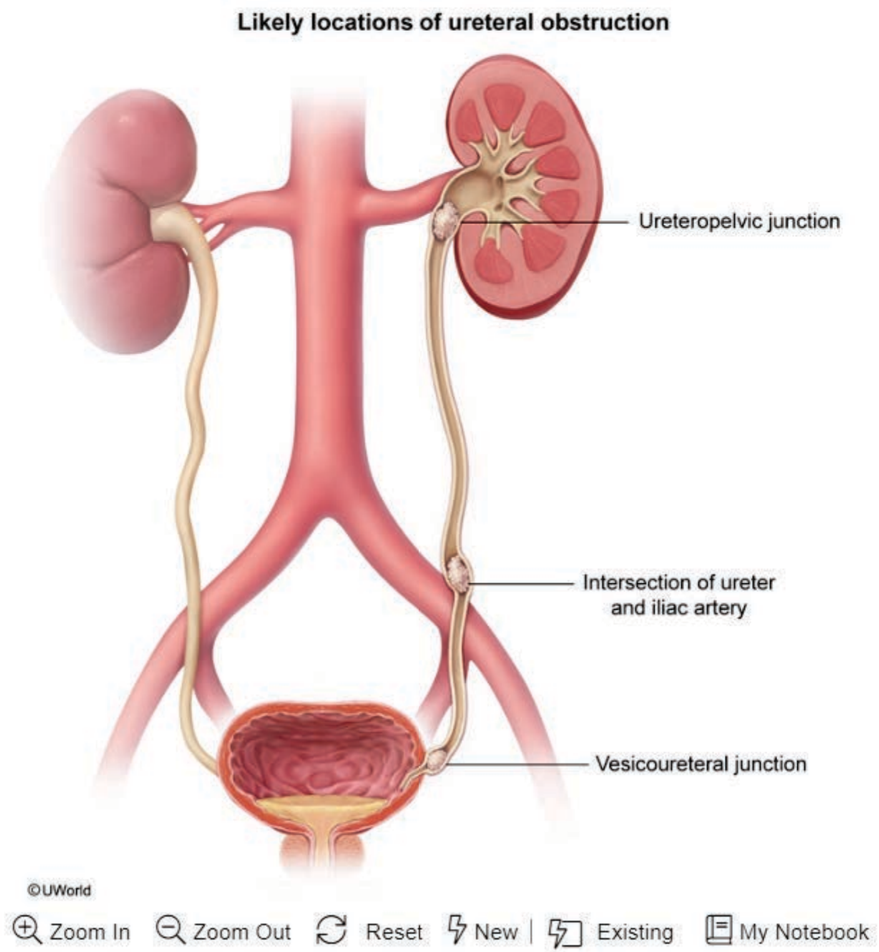
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A 50-year-old man is seen in the office for new-onset constipation. Family history is unremarkable. Vital signs are within normal limits. Physical examination reveals normal findings. Serum laboratory results are as follows:

Creatinine	1.1 mg/dL
Calcium	11.3 mg/dL
Phosphorus, inorganic	1.9 mg/dL
Parathyroid hormone	98 pg/mL (normal: 10-65)

Which of the following is the most likely mechanism causing this patient's low serum phosphate?

- A. Decreased phosphate reabsorption in proximal tubules
- B. Increased bone deposition of phosphorus
- C. Increased fecal loss of phosphorus
- D. Increased phosphate secretion in distal tubules
- E. Transcellular shift of phosphorus into the cells

Submit

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Calcium	11.3 mg/dL
Phosphorus, inorganic	1.9 mg/dL
Parathyroid hormone	98 pg/mL (normal: 10-65)

Which of the following is the most likely mechanism causing this patient's low serum phosphate?

- ✓ A. Decreased phosphate reabsorption in proximal tubules (72%)
- ✗ B. Increased bone deposition of phosphorus (2%)
- C. Increased fecal loss of phosphorus (3%)
- D. Increased phosphate secretion in distal tubules (18%)
- E. Transcellular shift of phosphorus into the cells (2%)

Incorrect
Correct answer
A

72%
Answered correctly

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Explanation

Parathyroid hormone, calcium, and phosphorus

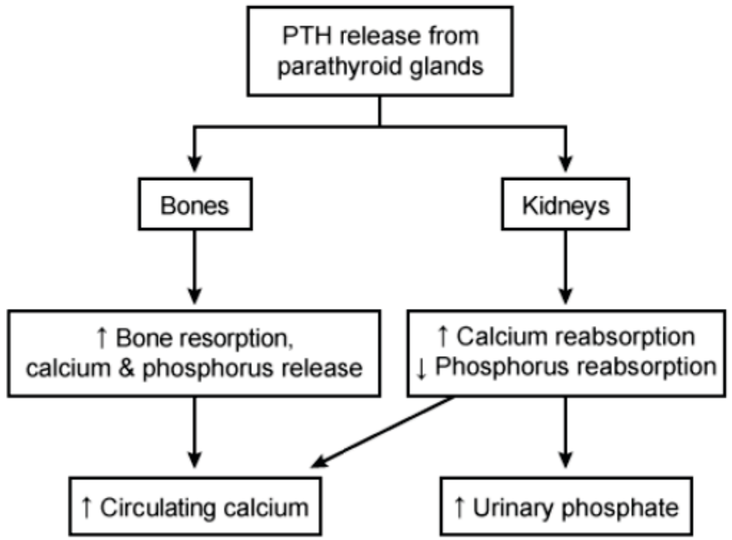


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B. Increased bone deposition of phosphorus (2%)

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Parathyroid hormone, calcium, and phosphorus



PTH = parathyroid hormone.

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PTH = parathyroid hormone

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PTH = parathyroid hormone.
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This patient has mild hypercalcemia associated with hypophosphatemia, suggesting an excess of **parathyroid hormone (PTH)**. PTH is released in response to hypocalcemia and acts to **raise plasma calcium** and **lower plasma phosphorus** by the following mechanisms:

- In the bones, PTH indirectly activates osteoclasts to increase bone resorption, releasing calcium and phosphorus.
- In the kidneys, PTH **decreases proximal tubular reabsorption of phosphate** and increases calcium reabsorption in the distal convoluted tubule and collecting duct.
- PTH upregulates 1-alpha-hydroxylase in the kidney, which converts 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (the more active form), further increasing calcium absorption in the kidneys and small intestine.

Primary hyperparathyroidism is characterized by **over-secretion of PTH**, despite normal (or elevated) calcium levels. Causes include parathyroid adenoma, multiglandular parathyroid hyperplasia, or (rarely) parathyroid carcinoma. Manifestations are largely related to hypercalcemia and include **constipation**, abdominal pain, kidney stones, fatigue, and bone pain.

(Choice B) Hungry bone syndrome can occur after resection of a parathyroid adenoma in patients with primary hyperparathyroidism. The abrupt loss of resorptive stimulus can lead to rapid bone formation, resulting in hypophosphatemia and hypocalcemia. However, this patient has not yet undergone parathyroidectomy.

(Choice C) Phosphate binders (eg, sevelamer) are synthetic polymers that bind intestinal phosphate and are subsequently eliminated in the feces. They are used to lower plasma phosphorus in patients with hyperphosphatemia due to chronic kidney disease. In patients not taking these medications, most phosphorus is eliminated in the urine and very little in the feces.

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intestine.

Primary hyperparathyroidism is characterized by **over-secretion of PTH**, despite normal (or elevated) calcium levels. Causes include parathyroid adenoma, multiglandular parathyroid hyperplasia, or (rarely) parathyroid carcinoma. Manifestations are largely related to hypercalcemia and include **constipation**, abdominal pain, kidney stones, fatigue, and bone pain.

(Choice B) Hungry bone syndrome can occur after resection of a parathyroid adenoma in patients with primary hyperparathyroidism. The abrupt loss of resorptive stimulus can lead to rapid bone formation, resulting in hypophosphatemia and hypocalcemia. However, this patient has not yet undergone parathyroidectomy.

(Choice C) Phosphate binders (eg, sevelamer) are synthetic polymers that bind intestinal phosphate and are subsequently eliminated in the feces. They are used to lower plasma phosphorus in patients with hyperphosphatemia due to chronic kidney disease. In patients not taking these medications, most phosphorus is eliminated in the urine and very little in the feces.

(Choice D) Phosphate is filtered at the glomerulus and reabsorbed in the absence of PTH. Hyperparathyroidism results in decreased reabsorption in the proximal tubule; however, phosphate is not secreted.

(Choice E) Reintroduction of carbohydrates in chronically malnourished patients (eg, anorexia nervosa) leads to a surge in insulin, which drives phosphorus intracellularly for use in cellular metabolism (ie, ATP production). This causes refeeding syndrome, characterized by severe hypophosphatemia, weakness, rhabdomyolysis, and arrhythmias. This patient's mild hypercalcemia and constipation are more suggestive of hyperparathyroidism.

Educational objective:
Primary hyperparathyroidism is characterized by oversecretion of parathyroid hormone despite normal (or elevated) serum calcium levels. Parathyroid hormone raises serum calcium and lowers serum phosphorus by increasing bone resorption (freeing calcium and phosphate), increasing renal reabsorption of calcium, and decreasing proximal tubular reabsorption of phosphate.

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Scientists investigating the specifics of kidney function in humans develop a new technique allowing them to measure the concentration of various compounds along the length of the proximal tubule. During an experiment, they record the concentrations of several endogenous substances in the fluid traversing the proximal tubule. Tubular fluid/plasma ultrafiltrate concentration ratios for the measured substances are shown in the image below:

Which of the following substances are most likely to produce lines 2 and 4, respectively?

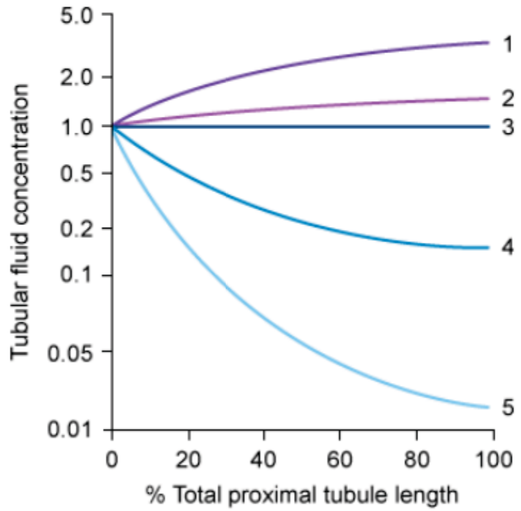
- A. Bicarbonate, sodium
- B. Creatinine, amino acids
- C. Creatinine, glucose
- D. Potassium, chloride
- E. Urea, bicarbonate

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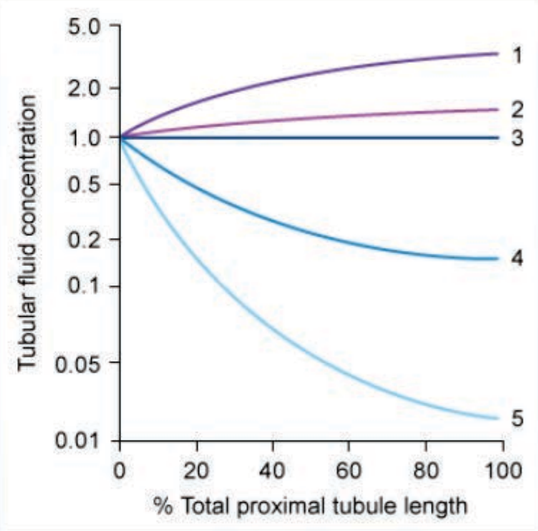


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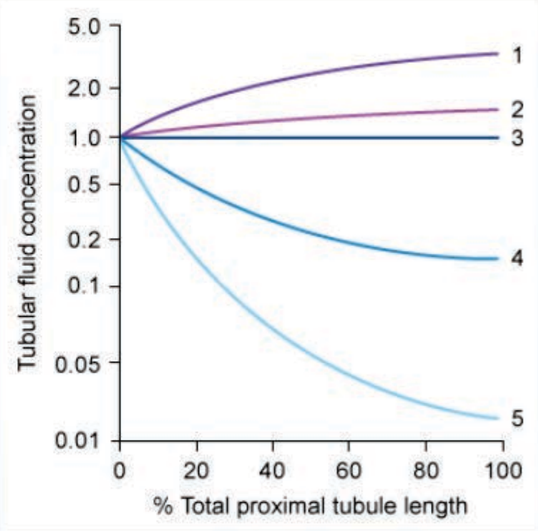
Which of the following substances are most likely to produce lines 2 and 4, respectively?

- A. Bicarbonate, sodium
- B. Creatinine, amino acids
- C. Creatinine, glucose
- D. Potassium, chloride
- E. Urea, bicarbonate

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Which of the following substances are most likely to produce lines 2 and 4, respectively?

- A. Bicarbonate, sodium (11%)
- ✗ B. Creatinine, amino acids (22%)
- C. Creatinine, glucose (20%)
- D. Potassium, chloride (8%)
- ✓ E. Urea, bicarbonate (37%)

Incorrect
Correct answer
E

37%
Answered correctly

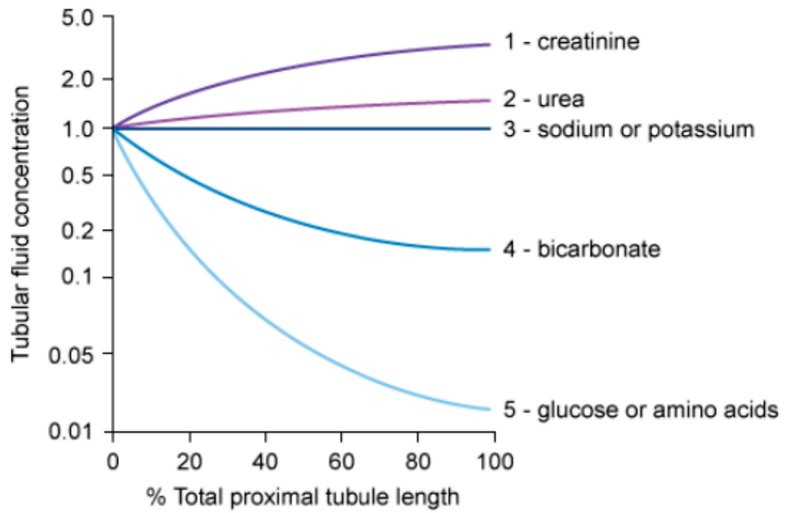
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E. Urea, bicarbonate (37%)

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- **Line 1** represents **creatinine**, which is freely filtered in the glomerulus, as well as actively secreted and not

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The tubular fluid/plasma ultrafiltrate value is calculated by dividing the tubular fluid concentration of a given substance in the proximal tubule by the initial concentration of that substance within Bowman's capsule. Therefore, an **upward (positive) slope** indicates an **increasing concentration** of that substance as fluid moves toward distal parts of the tubule, which is usually the result of **secretion or nonreabsorption** of that substance. A **downward slope** indicates **active reabsorption** of that substance in the proximal tubule.

- **Line 1** represents **creatinine**, which is freely filtered in the glomerulus, as well as actively secreted and not reabsorbed along the proximal tubule, resulting in a rapidly increasing concentration in the tubular fluid.
- **Line 2** represents **urea**, which is freely filtered from the glomerular capillaries and is poorly reabsorbed from the proximal tubule, resulting in increasing concentrations along the proximal tubule but less so than with creatinine. Renal handling of urea varies throughout the different tubular systems, but it is ultimately secreted in very high concentrations because it is a waste product of metabolism.
- **Line 3** represents **sodium or potassium**, which is reabsorbed in concentrations approximately equal with water in the proximal tubule, resulting in no concentration change along the proximal tubule.
- **Line 4** represents **bicarbonate**, which is actively reabsorbed in the proximal tubule due to the activity of carbonic anhydrase along the brush border. This reabsorption causes the concentration of bicarbonate to decrease as fluid runs along the proximal tubule.
- **Line 5** represents **glucose or amino acids**, which are avidly reabsorbed in the proximal tubule.

In summary, the concentrations of creatinine and urea increase along the proximal tubule due to active secretion or poor reabsorption, respectively, whereas the concentrations of bicarbonate, glucose, and amino acids decrease due to active reabsorption. Sodium and potassium are reabsorbed with water in the proximal tubule, resulting in no concentration change.

Educational objective:
The concentrations of creatinine and urea increase as fluid runs along the proximal tubule, whereas the

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A 68-year-old woman is brought to the emergency department due to worsening lethargy. Her family states that the patient has had headache and nausea for the past several days, and today she was confused and lethargic. Medical history is significant for seizure disorder, hypertension, type 2 diabetes mellitus, and bipolar disorder, for which she is on a number of medications. Vital signs are within normal limits. On physical examination, the patient is somnolent and responds to painful stimuli only. Mucous membranes are moist and jugular venous pressure is normal. The lungs are clear to auscultation and heart sounds are normal. There is no extremity edema. Laboratory evaluation reveals severe hyponatremia with a serum sodium of 118 mEq/L; blood urea nitrogen and serum creatinine are within normal limits. Serum osmolality is low and urine osmolality is high. Which of the following medications is the most likely cause of this patient's condition?

- A. Canagliflozin
- B. Carbamazepine
- C. Furosemide
- D. Lithium
- E. Spironolactone

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- ✗ A. Canagliflozin (9%)
- ✓ B. Carbamazepine (27%)
- C. Furosemide (17%)
- D. Lithium (33%)
- E. Spironolactone (9%)

Incorrect
Correct answer
B

27%
Answered correctly

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Explanation

Syndrome of inappropriate antidiuretic hormone (SIADH)

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Explanation

Syndrome of inappropriate antidiuretic hormone (SIADH)	
Pathophysiology	• Uncontrolled secretion of ADH • Leads to water retention & impaired urinary water excretion
Causes	• CNS disturbances (stroke, hemorrhage, trauma) • Medications (eg, carbamazepine, SSRIs, NSAIDs) • Lung disease (eg, pneumonia) • Malignancy (eg, small-cell lung cancer)
Clinical findings	• Nausea, forgetfulness (mild hyponatremia) • Seizures, coma (severe hyponatremia) • Euvolemia (eg, moist mucous membranes, no edema, no JVD)
Laboratory findings	• Hyponatremia • Low serum osmolality • High urine osmolality • High urine sodium
ADH = antidiuretic hormone; **JVD** = jugular venous distension; **SSRIs** = selective serotonin reuptake inhibitors.	

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selective serotonin reuptake inhibitors.

This patient has symptomatic hyponatremia (eg, somnolence, lethargy) and her laboratory studies (eg, low serum osmolality, high urine osmolality) are consistent with the syndrome of inappropriate antidiuretic hormone secretion (**SIADH**). Antidiuretic hormone (ADH) is released by the hypothalamus and posterior pituitary and stimulates the renal collecting ducts to reabsorb water into the systemic circulation. Patients with excessive ADH activity (ie, SIADH) typically have the following manifestations:

- Serum sodium and osmolality decrease, leading to **hypotonic hyponatremia**.
- Urinary water excretion decreases, increasing urine osmolality and creating a **concentrated urine**.
- **Clinical euvolemia**, which is reflected by an absence of edema, lung crackles, and jugular venous distention (signs of hypervolemia) along with absence of dry mucous membranes and elevated blood urea nitrogen (BUN) and creatinine (signs of hypovolemia).

In this case, the patient's SIADH is likely due to **carbamazepine**, an antiepileptic drug that induces ADH production and increases renal sensitivity to ADH. Other medications associated with SIADH include antidepressants (eg, selective serotonin reuptake inhibitors and tricyclic antidepressants), certain antidiabetic drugs (eg, chlorpropamide), and recreational drugs (eg, MDMA [ie, ecstasy]).

(Choice A) Canagliflozin is a diabetic medication that inhibits sodium-glucose cotransporter 2 in the renal proximal tubule, increasing urinary glucose excretion. Canagliflozin is linked to urinary tract infections and hypotension, but not SIADH.

(Choices C and E) Furosemide and spironolactone are often used in combination to treat severe heart failure. Furosemide reduces sodium reabsorption in the loop of Henle, increasing sodium and water excretion. Spironolactone blocks the mineralocorticoid receptor, which increases sodium excretion and potassium reabsorption. Both diuretics can induce hyponatremia; however, patients are typically also hypovolemic (eg, with dry mucous membranes and elevated BUN and creatinine). This patient's euvolemia and normal BUN and

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(signs of hypervolemia) along with absence of dry mucous membranes and elevated blood urea nitrogen (BUN) and creatinine (signs of hypovolemia).

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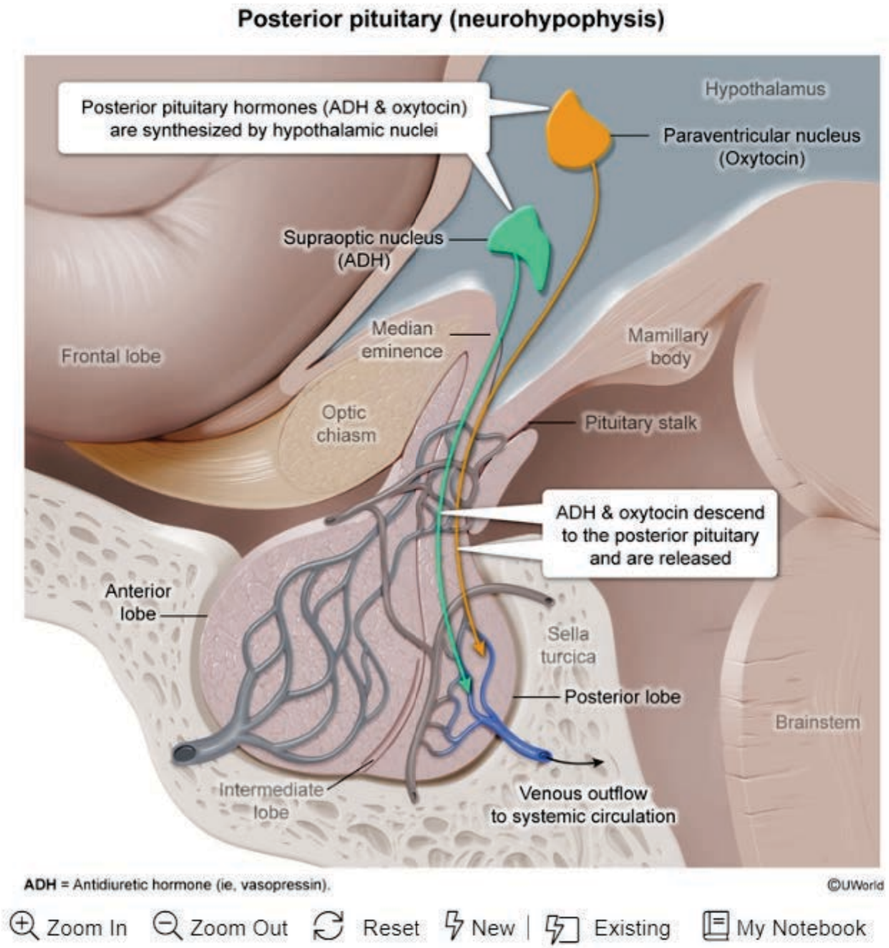
(Choice D) Lithium can cause ADH resistance in the renal collecting ducts, resulting in nephrogenic diabetes insipidus. In this condition, water cannot be reabsorbed; urine osmolality is low (dilute urine) and serum sodium and osmolality increase. This patient has an opposite picture (high urine osmolality, low serum sodium and osmolality), indicating SIADH.

Educational objective:
The syndrome of inappropriate antidiuretic hormone (SIADH) presents with hypotonic hyponatremia (ie, low serum osmolality and serum sodium), concentrated urine (ie, high urine osmolality), and euvolemia. Carbamazepine can cause SIADH by increasing antidiuretic hormone (ADH) secretion and renal sensitivity to ADH.

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Clinical findings	• Euvolemia (eg, moist mucous membranes, no

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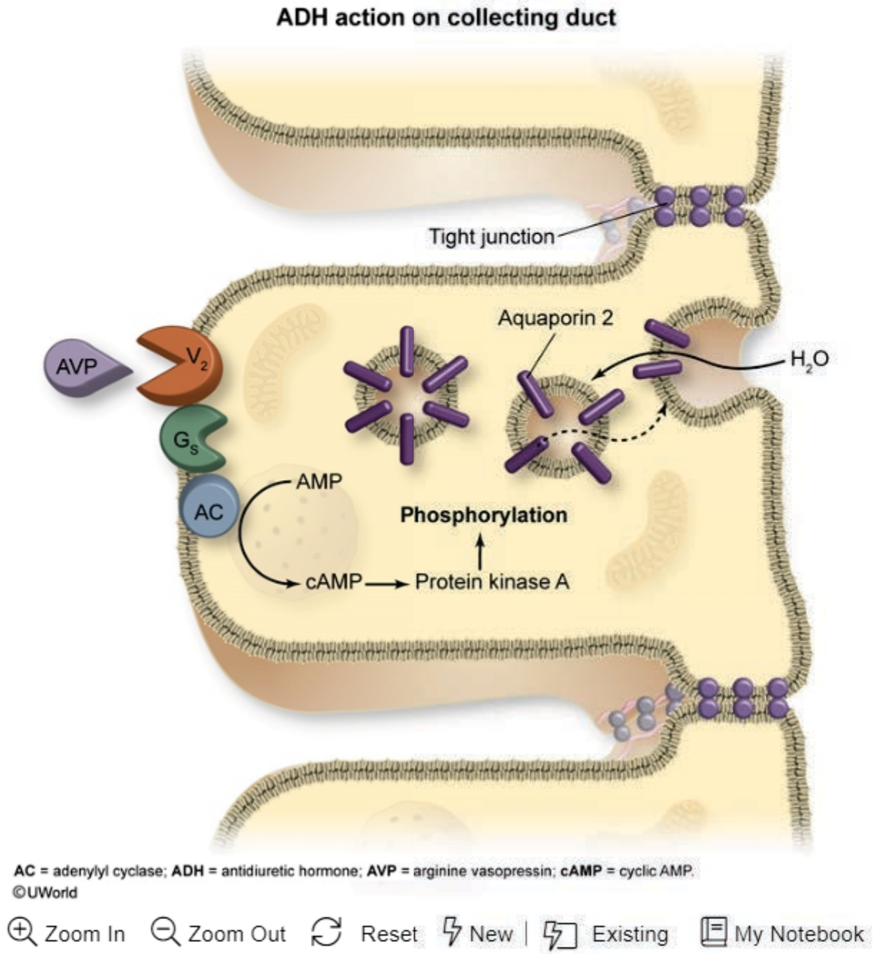
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chlorpropamide), and recreational drugs (eg, MDMA [ie, ecstasy]).

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Clinical findings	• Euvolemia (eg, moist mucous membranes, no

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AC = adenylyl cyclase; **ADH** = antidiuretic hormone; **AVP** = arginine vasopressin; **cAMP** = cyclic AMP.
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A 4-month-old girl is diagnosed with a febrile urinary tract infection. A voiding cystourethrogram shows retrograde urine flow into the right ureter but no associated ureteral dilation. One year later, a voiding cystourethrogram is repeated and shows no abnormalities. Which of the following is the most likely cause of this infant's presentation?

- A. Congenital short intravesical ureter length
- B. Damage to the rectovaginal septum
- C. Obstruction due to a renal stone
- D. Presence of a posterior urethral valve

Submit

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- ✓ A. Congenital short intravesical ureter length (56%)
- ✗ B. Damage to the rectovaginal septum (2%)
- C. Obstruction due to a renal stone (8%)
- D. Presence of a posterior urethral valve (32%)

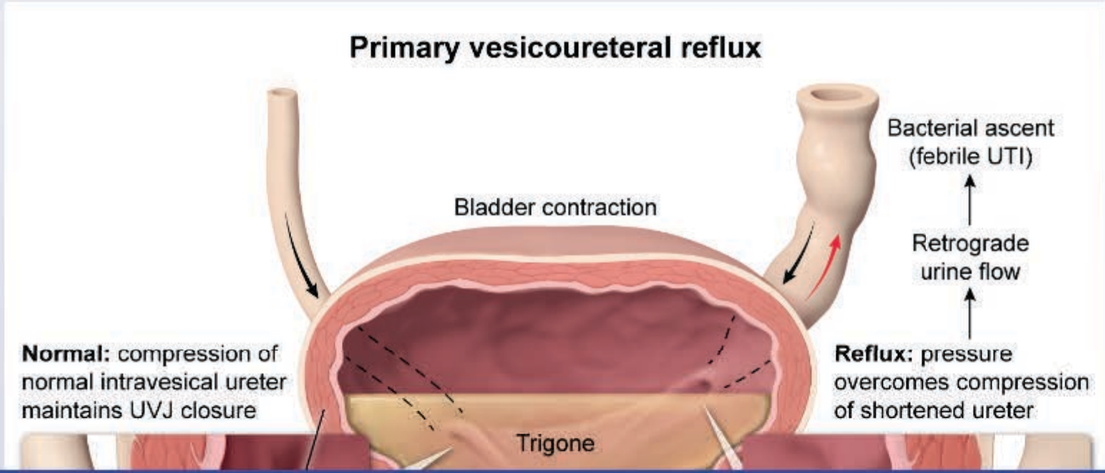
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56%
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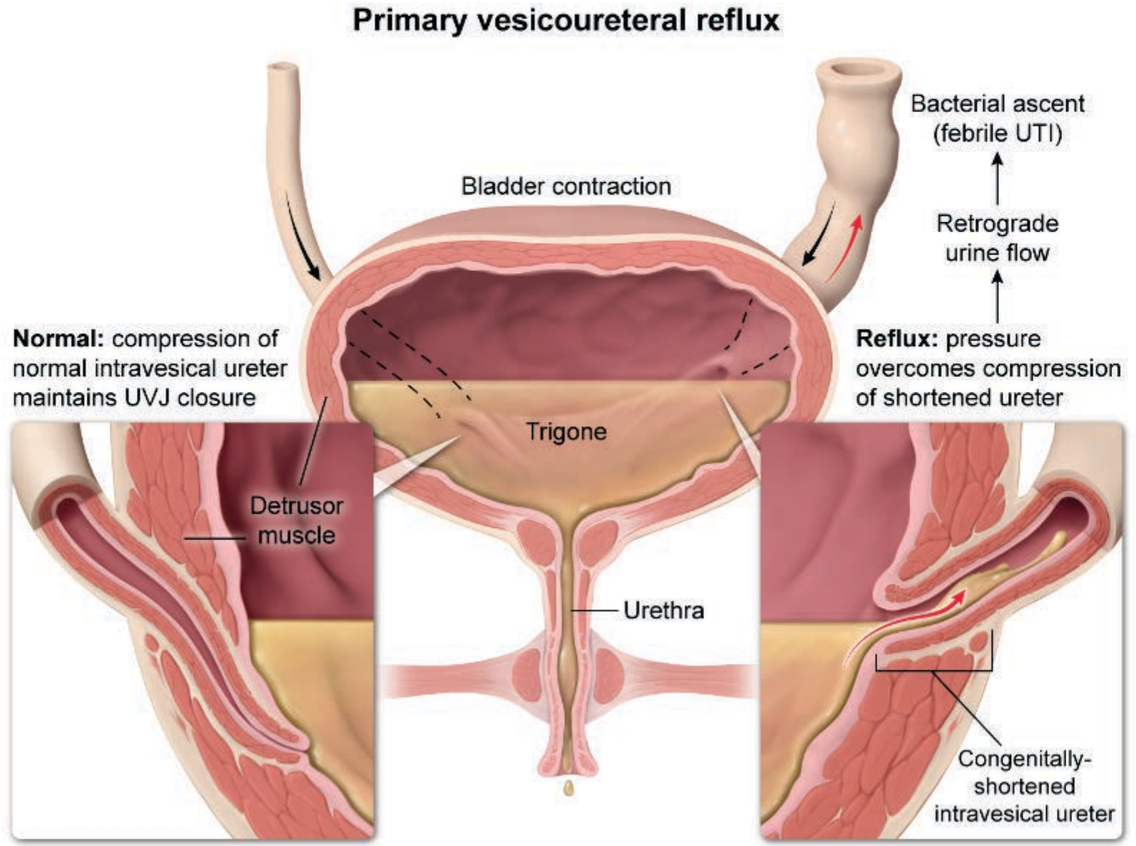
Explanation



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A 4-month-old girl is diagnosed with a febrile urinary tract infection. A voiding cystourethrogram shows retrograde urine
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This patient has **vesicoureteral reflux** (VUR), which is characterized by abnormal retrograde flow of urine into the ureter. Most cases of VUR occur due to a congenitally **shortened intravesical ureter** (ie, the segment of ureter that passes through the bladder wall).

Contraction of the detrusor muscle during micturition not only increases pressure within the bladder, it also compresses the intravesical segment of the ureter, which maintains closure of the ureterovesical junction (UVJ). If the intravesical ureter length is too short, the increased urine pressure may overcome the compression effect on the ureter, allowing **retrograde urine flow** (potentially causing bacterial ascent and febrile urinary tract infection [ie, pyelonephritis]).

The severity of VUR is variable based on the degree of ureter and kidney damage (eg, ureteral dilation, hydronephrosis, nephropathy). Spontaneous resolution occurs in most patients with mild VUR, such as this patient, because the intravesical ureter length increases with patient growth.

(Choice B) The rectovaginal septum is a fascial layer that separates the posterior wall of the vagina from the anterior wall of the rectum. Damage to this area typically occurs during the birthing process, resulting in bowel (not bladder) dysfunction.

(Choice C) Although renal stones may obstruct urine flow, they do not cause retrograde urine flow.

(Choice D) Posterior urethral valves occur due to abnormal development of the mesonephric (Wolffian) duct. They can obstruct urine flow through the urethra; subsequent increase in intravesical pressure may cause reflux of urine into the ureter (ie, VUR). However, VUR secondary to posterior urethral valves does not resolve spontaneously and almost exclusively occurs in boys.

Educational objective:
Vesicoureteral reflux typically occurs due to a congenitally shortened intravesical ureter length, which prevents complete closure of the ureterovesical junction and allows retrograde urine flow into the ureter during micturition. Most cases resolve spontaneously as the length of the intravesical ureter increases with patient growth.

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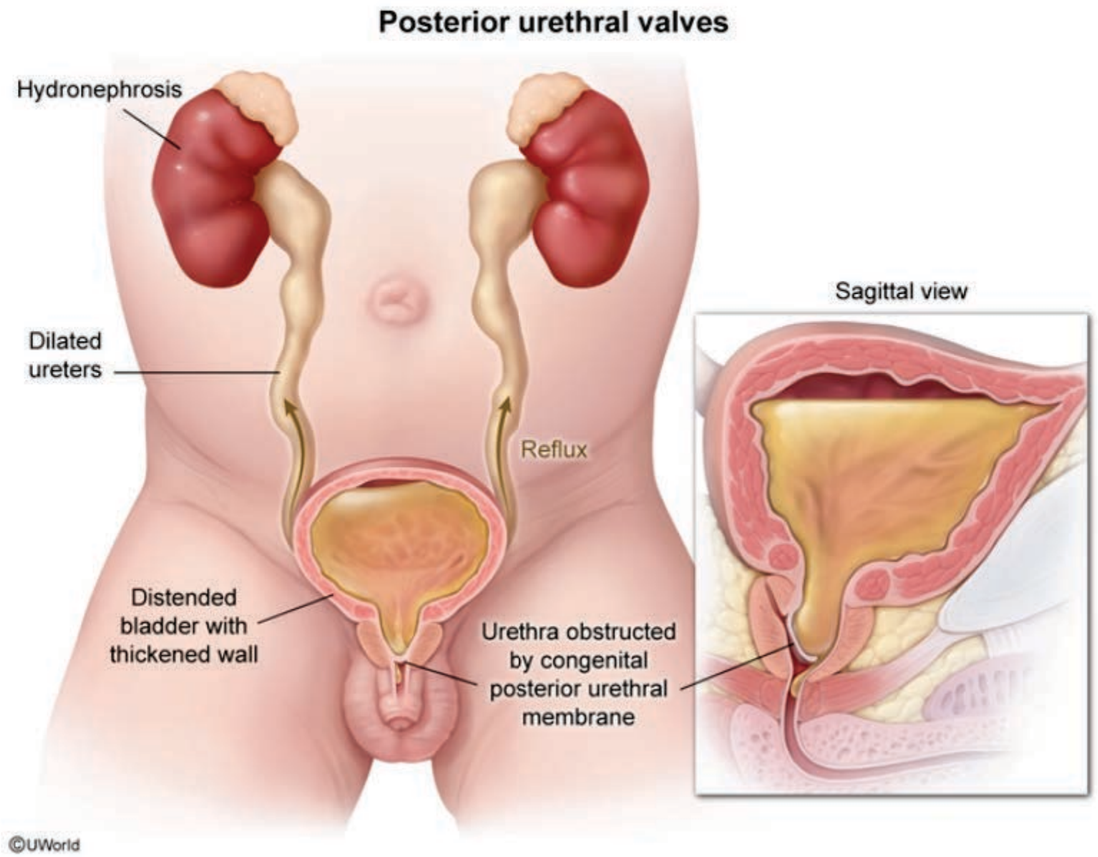
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A 52-year-old postmenopausal woman comes to the office due to urine leakage with coughing and sneezing. She has no dysuria, urgency, or changes in urinary frequency. The patient has had 3 spontaneous vaginal deliveries. On pelvic examination, there is mild vulvovaginal atrophy and anterior vaginal wall prolapse. The remainder of the physical examination is normal. The patient is advised to perform exercises to strengthen her pelvic floor as part of treatment for her symptoms. Which of the following structures is the most likely target of the exercise?

- A. Bulbospongiosus muscle
- B. Detrusor muscle
- C. Internal urethral sphincter
- D. Levator ani muscle complex
- E. Uterosacral ligament

Submit

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- A. Bulbospongiosus muscle (7%)
- ✗ B. Detrusor muscle (9%)
- C. Internal urethral sphincter (12%)
- ✓ D. Levator ani muscle complex (69%)
- E. Uterosacral ligament (1%)

Incorrect
Correct answer
D

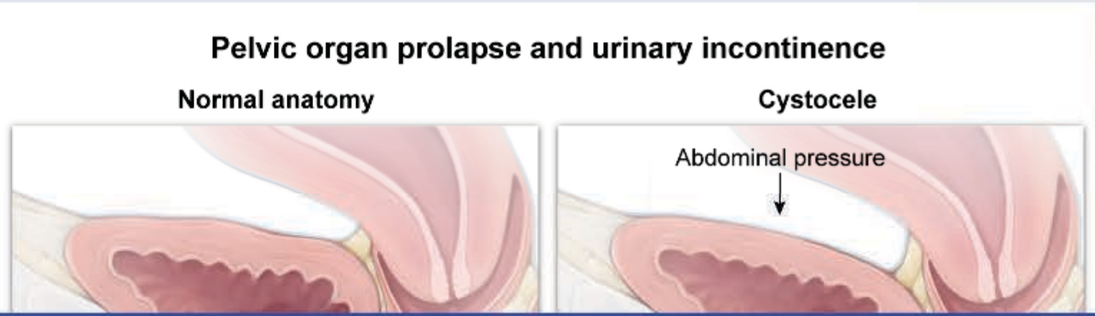
69%
Answered correctly

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Explanation

Pelvic organ prolapse and urinary incontinence

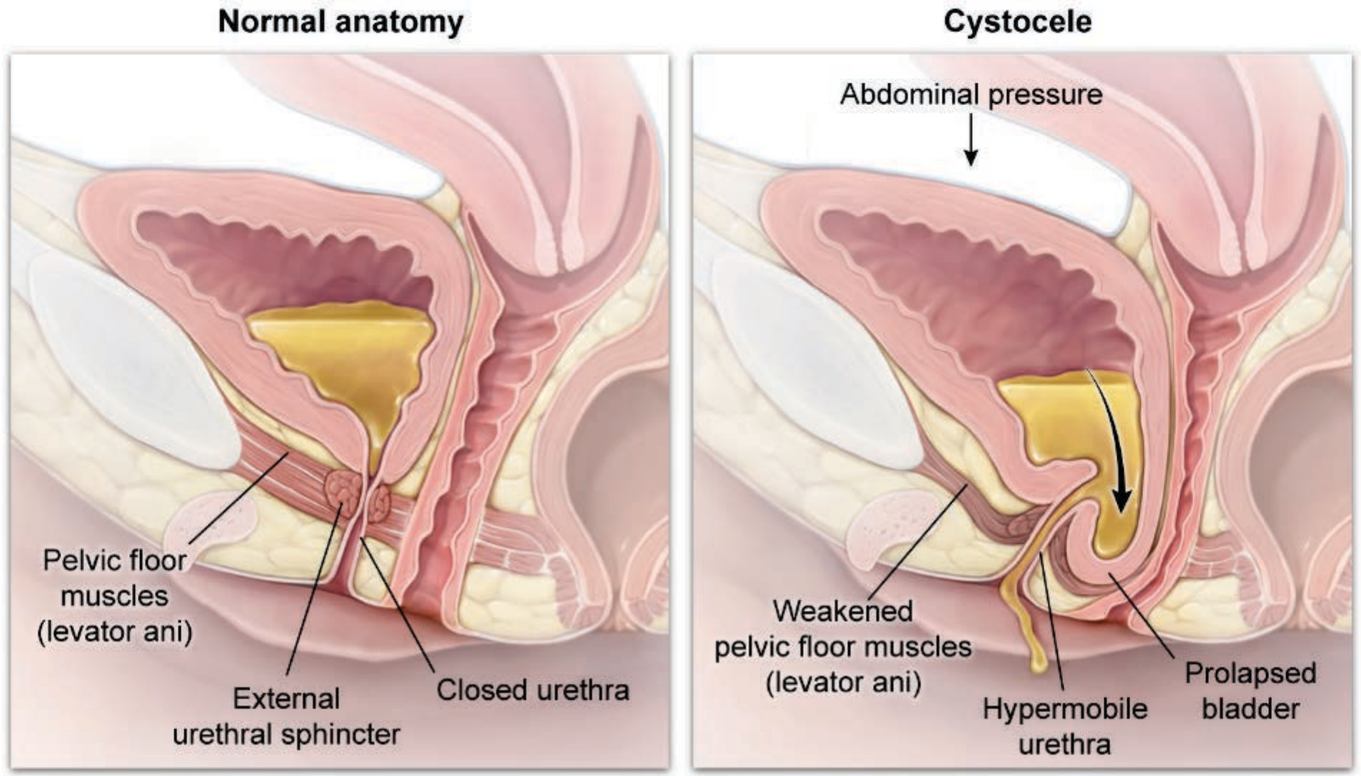


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Pelvic organ prolapse and urinary incontinence



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urethra

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This patient's loss of urine with increased intraabdominal pressure (eg, coughing, sneezing) is due to **stress urinary incontinence** (SUI). The bladder and urethra are typically maintained in a normal anatomic position by the pelvic floor muscles known as the **levator ani muscle complex** (ie, iliococcygeus, pubococcygeus, puborectalis), which form a U-shaped sling around the pelvic viscera for pelvic support.

Patients develop SUI due to chronic pressure (eg, obesity) or injury (eg, **multiple vaginal deliveries**) affecting the levator ani muscle complex, which results in **pelvic floor weakness** and laxity. Chronic pelvic floor laxity contributes to **urethral hypermobility**, in which the pelvic floor muscles cannot stabilize and fully compress (close) the urethra against the anterior vaginal wall during times of increased intraabdominal pressure (eg, coughing). Pelvic floor weakness can also lead to herniation of the bladder into the vagina and **anterior vaginal wall prolapse** (cystocele).

First-line treatment of SUI is **pelvic floor muscle (Kegel) exercises**, which repeatedly activate and release the levator ani muscle complex to gradually strengthen and stabilize the pelvic floor. The strengthened pelvic musculature provides a stable base for urethral compression, thereby maintaining continence.

(Choice A) The bulbospongiosus muscle is part of the superficial urogenital triangle of the perineum. It constricts the vaginal orifice and is commonly damaged during vaginal delivery. Because it is a superficial muscle, strengthening it does not improve pelvic floor support or reduce SUI.

(Choices B and C) Detrusor muscle overactivity results in urge incontinence (eg, the sudden need to urinate followed by immediate, involuntary loss of urine) rather than SUI, while stimulation of the internal urethral sphincter helps prevent urine leakage. Both are smooth muscles (ie, controlled by the autonomic nervous system); therefore, they cannot be voluntarily exercised for symptom improvement.

(Choice E) The uterosacral ligaments run along the lateral pelvic wall and elevate the uterus and vaginal apex by attaching to the sacrum. Weakening of these ligaments contributes to uterine prolapse but does not directly cause SUI or anterior vaginal wall prolapse.

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(Choice A) The bulbospongiosus muscle is part of the superficial urogenital triangle of the perineum. It constricts the vaginal orifice and is commonly damaged during vaginal delivery. Because it is a superficial muscle, strengthening it does not improve pelvic floor support or reduce SUI.

(Choices B and C) Detrusor muscle overactivity results in urge incontinence (eg, the sudden need to urinate followed by immediate, involuntary loss of urine) rather than SUI, while stimulation of the internal urethral sphincter helps prevent urine leakage. Both are smooth muscles (ie, controlled by the autonomic nervous system); therefore, they cannot be voluntarily exercised for symptom improvement.

(Choice E) The uterosacral ligaments run along the lateral pelvic wall and elevate the uterus and vaginal apex by attaching to the sacrum. Weakening of these ligaments contributes to uterine prolapse but does not directly cause SUI or anterior vaginal wall prolapse.

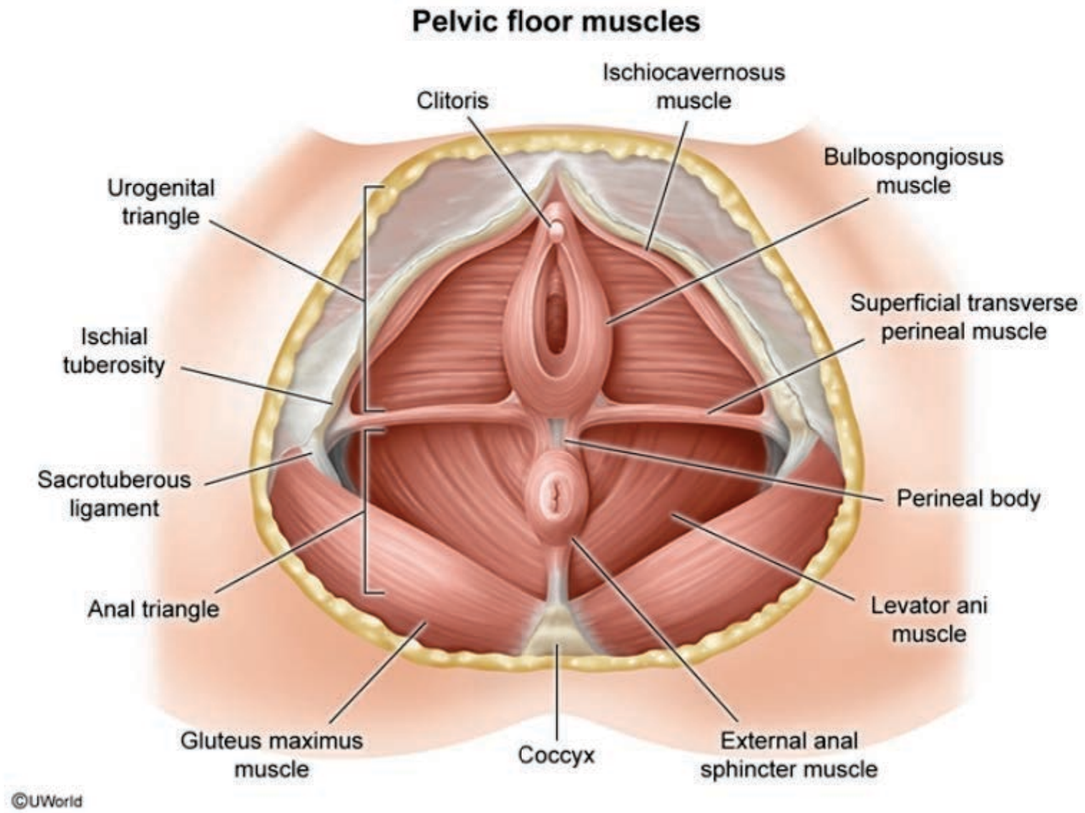
Educational objective:
Stress urinary incontinence is involuntary urine leakage with increased intraabdominal pressure (eg, coughing, sneezing). Pelvic floor muscle (Kegel) exercises target and strengthen the levator ani muscle complex, improving support around the urethra and bladder and symptoms of stress urinary incontinence.

References

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the pelvic floor muscles known as the **levator ani muscle complex** (ie, iliococcygeus, pubococcygeus,

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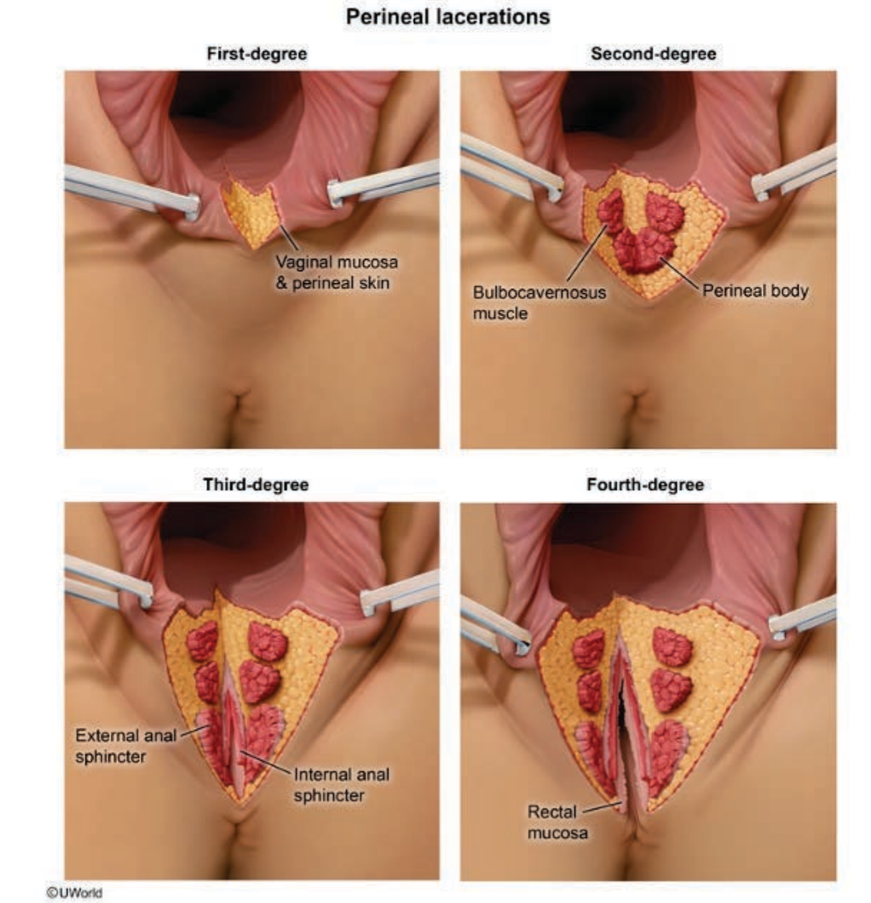
Edu

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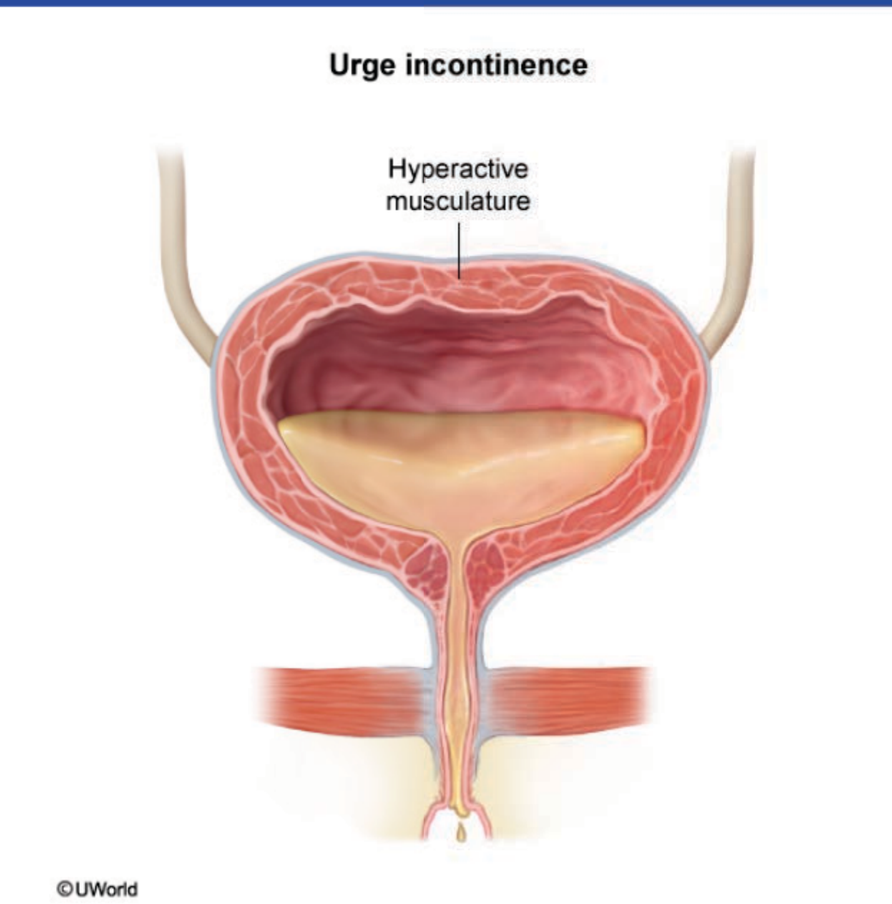
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A 3-month-old boy is brought to the office due to fussiness, poor weight gain, and polyuria. Urine volume is 700-800 mL/day. The patient's maternal grandfather has polydipsia and polyuria. Serum sodium is 151 mEq/L. Genetic testing reveals a vasopressin-2 receptor mutation. Which of the following additional findings is most likely to be seen in this patient?

	Serum osmolality	Urine osmolality after water deprivation	Change in urine osmolality with desmopressin administration
○ A.	High	Low	No change
○ B.	High	High	No change
○ C.	High	Low	Increased
○ D.	Low	High	No change
○ E.	Low	Low	No change
○ F.	Low	Low	Increased

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	Serum osmolality	Urine osmolality after water deprivation	Change in urine osmolality with desmopressin administration	
✓ A.	High	Low	No change	(70%)
B.	High	High	No change	(12%)
C.	High	Low	Increased	(7%)
D.	Low	High	No change	(4%)
E.	Low	Low	No change	(5%)
F.	Low	Low	Increased	(1%)

Correct

70% Answered correctly

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Explanation

Polyuria & polydipsia

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Polyuria & polydipsia			
	Baseline serum osmolality	Water deprivation test	
		Urine osmolality after water deprivation	Urine osmolality with vasopressin injection
Normal	Normal	Increased	No change
Central diabetes insipidus	High	No change	Increased
Nephrogenic diabetes insipidus	High	No change	No change
Primary polydipsia	Low	Increased	No change

This patient with a vasopressin-2 (V2) receptor mutation has polyuria and hypernatremia, findings which are consistent with congenital **nephrogenic diabetes insipidus** (DI).

V2 receptors are located in the renal cortical collecting ducts. When serum osmolality rises (eg, water deprivation, dehydration), there is increased release of antidiuretic hormone (ADH, vasopressin) which activates V2 receptors to reabsorb water into the systemic circulation. Water reabsorption leads to concentrated urine (low urinary volume, high urine osmolality) and lower serum osmolality.

Mutations that impair normal V2 receptor function result in nephrogenic DI (**ADH resistance**). Following water deprivation, the collecting ducts are unable to reabsorb water despite high circulating ADH levels, leading to ongoing urinary water losses. Therefore, nephrogenic DI manifests with large volumes of abnormally **dilute urine** (ie, polyuria with low urine osmolality), **high serum osmolality** (ie, hypernatremia), and dehydration.

High serum osmolality, polyuria, and dilute urine also occur in central DI, which is caused by deficient ADH

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High serum osmolality, polyuria, and dilute urine also occur in central DI, which is caused by deficient ADH production by the hypothalamus. As with nephrogenic DI, urine remains abnormally dilute after water deprivation. However, **challenge with desmopressin** (an analogue of ADH) can differentiate between central and nephrogenic DI:

- In nephrogenic DI, desmopressin cannot correct the underlying ADH resistance. Therefore, **urine osmolality remains unchanged** (eg, low).
- In **central DI**, desmopressin corrects the underlying ADH deficiency. Therefore, **urine osmolality increases** following administration **(Choice C)**.

(Choice B) High baseline serum osmolality and high urine osmolality can be seen in states of marked hyperglycemia with glucosuria (ie, solute diuresis). Although polyuria can occur, the ADH response remains intact, so urine osmolality will be high with water deprivation.

(Choice D) Primary polydipsia can also result in polyuria with dilute urine. However, unlike DI, serum osmolality and sodium are low (due to excess water intake), and dilute urine represents an appropriate physiologic response.

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(ie, polyuria with low urine osmolality), **high serum osmolality** (ie, hypernatremia), and dehydration.

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(Choice D) Primary polydipsia can also result in polyuria with dilute urine. However, unlike DI, serum osmolality and sodium are low (due to excess water intake), and dilute urine represents an appropriate physiologic response. ADH response is intact, so urine osmolality is appropriately high following water deprivation. No additional change is seen with desmopressin because maximum ADH levels are reached with water deprivation.

(Choices E and F) This patient has visible signs of dehydration and hypernatremia; because sodium is a major determinant of serum osmolality, a high serum osmolality is expected.

Educational objective:
Vasopressin-2 receptor mutations are a cause of congenital nephrogenic diabetes insipidus, a condition in which renal resistance to antidiuretic hormone results in excessive urinary water losses. Expected findings include high baseline serum osmolality (typically with hypernatremia), persistently dilute urine after water deprivation (low urine osmolality), and lack of response to desmopressin.

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A previously healthy 45-year-old male undergoes an elective hernia repair under spinal anesthesia. Postoperatively, he complains of difficulty voiding. Bladder catheterization shows a post-void residual of 300cc of urine. This patient would most likely benefit from which of the following medications?

- A. Finasteride
- B. Phenylephrine
- C. Bethanechol
- D. Oxybutynin
- E. Imipramine

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A previously healthy 45-year-old male undergoes an elective hernia repair under spinal anesthesia. Postoperatively, he complains of difficulty voiding. Bladder catheterization shows a post-void residual of 300cc of urine. This patient would most likely benefit from which of the following medications?

- A. Finasteride (8%)
- ✗ B. Phenylephrine (4%)
- ✓ C. Bethanechol (75%)
- D. Oxybutynin (8%)
- E. Imipramine (3%)

Incorrect
Correct answer
C

75%
Answered correctly

03 secs
Time Spent

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Explanation

This patient most likely has postoperative urinary retention, which occurs in up to 25% of patients after lower abdominal surgery. A normal post-void residual urine volume in the bladder is less than 50cc. Anesthesia and analgesia contribute to all of the following: over-distention of the bladder, a decreased micturition reflex, decreased contractility of the bladder detrusor muscle, and incomplete emptying.

Contraction of the detrusor muscle is stimulated by muscarinic cholinergic agonists. Bethanechol, a muscarinic agonist, often improves bladder-emptying in patients with post-surgery urinary retention.

(Choice A) Finasteride is prescribed for patients with bladder outlet obstruction secondary to prostatic hypertrophy. Finasteride is a 5α-reductase inhibitor that decreases the local conversion of testosterone to

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This patient most likely has postoperative urinary retention, which occurs in up to 25% of patients after lower abdominal surgery. A normal post-void residual urine volume in the bladder is less than 50cc. Anesthesia and analgesia contribute to all of the following: over-distention of the bladder, a decreased micturition reflex, decreased contractility of the bladder detrusor muscle, and incomplete emptying.

Contraction of the detrusor muscle is stimulated by muscarinic cholinergic agonists. Bethanechol, a muscarinic agonist, often improves bladder-emptying in patients with post-surgery urinary retention.

(Choice A) Finasteride is prescribed for patients with bladder outlet obstruction secondary to prostatic hypertrophy. Finasteride is a 5α-reductase inhibitor that decreases the local conversion of testosterone to dihydrotestosterone in the prostate, thereby promoting shrinkage of the gland over 6 to 12 months. Since this patient's incomplete bladder emptying is due to weak detrusor muscle contraction rather than prostatic hypertrophy, finasteride would not be likely to improve his acute condition.

(Choice B) Phenylephrine is an alpha-agonist with some selectivity for α1 receptors. The occupation of α1 receptors in the bladder actually encourages the trigone and sphincter to contract. Phenylephrine promotes, rather than alleviates, urinary retention.

(Choice D) Oxybutynin is an antimuscarinic agent commonly used for urge incontinence. If given, it will worsen this patient's condition.

(Choice E) Imipramine has anticholinergic activity, and would thus worsen this patient's condition!

Educational Objective:
Postoperative urinary retention, with incomplete bladder emptying, is a common complication thought to involve decreased micturition reflex activity, decreased contractility of the bladder detrusor, and/or increased vesical sphincter tone. This condition may be treated with a muscarinic agonist (bethanechol) or an α1 blocking drug.

Pharmacology	Renal, Urinary Systems & Electrolytes	Urinary retention
Subject	System	Topic

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A 10-year-old boy is brought to the office due to dark brown urine that he first noticed yesterday after swimming practice. Blood pressure is 130/80 mm Hg. Physical examination is normal with the exception of bilateral periorbital edema. Laboratory results are as follows:

Serum chemistry	
Sodium	140 mEq/L
Potassium	4 mEq/L
Blood urea nitrogen	14 mg/dL
Creatinine	1.4 mg/dL
Creatine kinase	86 U/L
Urinalysis	
Protein	1+
Leukocyte esterase	negative
Nitrites	negative
White blood cells	1-2/hpf
Red blood cells	many/hpf
Casts	RBC casts

Which of the following is the most likely diagnosis?

A. Minimal change disease

B. Nephrolithiasis

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Potassium	4 mEq/L
Blood urea nitrogen	14 mg/dL
Creatinine	1.4 mg/dL
Creatine kinase	86 U/L

Urinalysis

Protein	1+
Leukocyte esterase	negative
Nitrites	negative
White blood cells	1-2/hpf
Red blood cells	many/hpf
Casts	RBC casts

Which of the following is the most likely diagnosis?

- A. Minimal change disease
- B. Nephrolithiasis
- C. Postinfectious glomerulonephritis
- D. Pyelonephritis
- E. Rhabdomyolysis

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Potassium	4 mEq/L
Blood urea nitrogen	14 mg/dL
Creatinine	1.4 mg/dL
Creatine kinase	86 U/L

Urinalysis

Protein	1+
Leukocyte esterase	negative
Nitrites	negative
White blood cells	1-2/hpf
Red blood cells	many/hpf
Casts	RBC casts

Which of the following is the most likely diagnosis?

- ✗ A. Minimal change disease (11%)
- B. Nephrolithiasis (0%)
- ✓ C. Postinfectious glomerulonephritis (67%)
- D. Pyelonephritis (1%)
- E. Rhabdomyolysis (18%)

Incorrect
Correct answer
C

67%
Answered correctly

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Explanation

Acute poststreptococcal glomerulonephritis	
Clinical features	• Can be asymptomatic • If symptomatic: ◦ Gross hematuria (tea- or cola-colored urine) ◦ Edema (periorbital, generalized) ◦ Hypertension
Laboratory findings	• Urinalysis: + protein, + blood, ± red blood cell casts • Serum: ◦ ↓ C3 & possible ↓ C4 ◦ ↑ Serum creatinine ◦ ↑ Anti-DNase B & ↑ AHase ◦ ↑ ASO & ↑ anti-NAD (from preceding pharyngitis)
AHase = antihyaluronidase; **anti-DNase B** = antideoxyribonuclease B; **anti-NAD** = antinicotinamide-adenine dinucleotidase; **ASO** = antistreptolysin O.	

This pediatric patient with periorbital edema, hypertension, and hematuria with red blood cell (RBC) casts, as well as mild proteinuria on urinalysis, most likely has **poststreptococcal glomerulonephritis**, a nonsuppurative complication of a pharyngeal or skin (eg, impetigo) infection. Infection with nephritogenic strains of group A *Streptococcus* (eg, *S pyogenes*) can induce formation of antigen-antibody complexes, which are deposited on the glomerular basement membrane. Subsequent activation of complement and inflammation can lead to **nephritic syndrome** 2-4 weeks after the infection; because of this delay, parents **may not report** the **inciting infection**.

Urine studies in nephritic syndrome typically reveal RBCs, mild protein, and **RBC casts** (indicating an intrarenal

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Urine studies in nephritic syndrome typically reveal RBCs, mild protein, and **RBC casts** (indicating an intrarenal process). Serum studies show elevated creatinine, **antistreptococcal antibodies** (from recent infection), and decreased C3 (glomerular complement deposition). Histologic findings include diffusely enlarged hypercellular glomeruli, RBC casts in nephron tubules, and interstitial inflammation and edema. Electron microscopy reveals electron-dense, **subepithelial deposits** or "humps" along the glomerular basement membrane that represent antigen-antibody complexes.

(Choice A) Minimal change disease is the most common cause of pediatric nephrotic syndrome. It is characterized by immune-related loss of the normal glomerular anionic charge (which prevents filtration of negatively charged albumin), leading to heavy proteinuria. However, hematuria and hypertension are unexpected.

(Choice B) Nephrolithiasis is a common cause of hematuria; however, the glomeruli are not involved, so RBC casts are unexpected. In addition, nephrolithiasis is rare in children and typically presents with back pain radiating to the groin.

(Choice D) Pyelonephritis is most commonly due to an ascending bacterial infection from the bladder. Microscopic urinalysis findings are similar to those of a urinary tract infection (eg, bacteria, leukocytes, nitrites, leukocyte esterase) with the addition of white blood cell casts.

(Choice E) Rhabdomyolysis can occur after strenuous exercise and results in muscle pain, elevated creatine kinase levels, and myoglobinuria (ie, positive urine dipstick for blood without RBCs on microscopy). This patient's normal creatine kinase level and the presence of many RBCs on urine microscopy are not suggestive of

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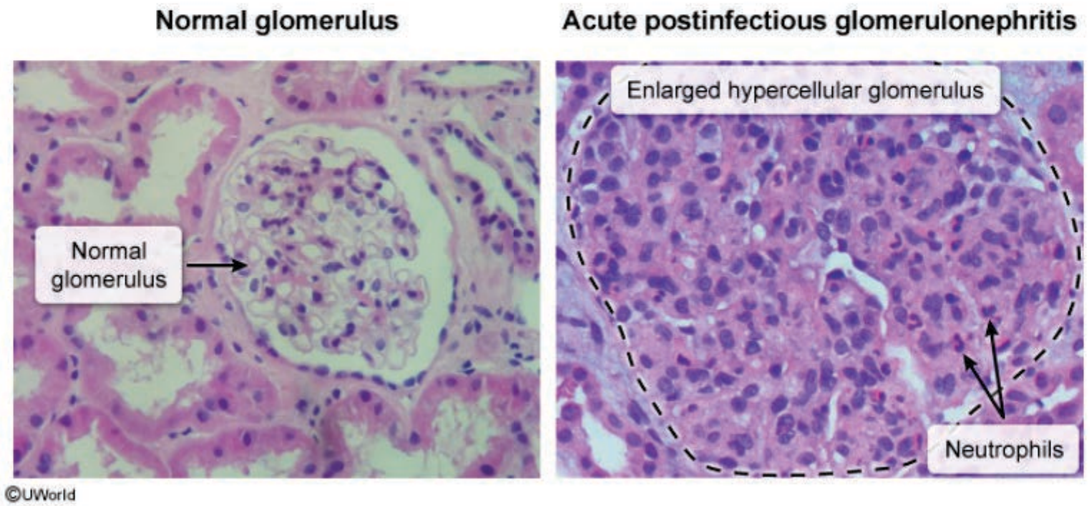
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Educational objective:
Poststreptococcal glomerulonephritis presents most commonly in children with hematuria, hypertension, and periorbital edema. Red blood cell casts and mild proteinuria may be present on urinalysis, and serum creatinine may be elevated.

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findings	○ ↑ Serum creatinine

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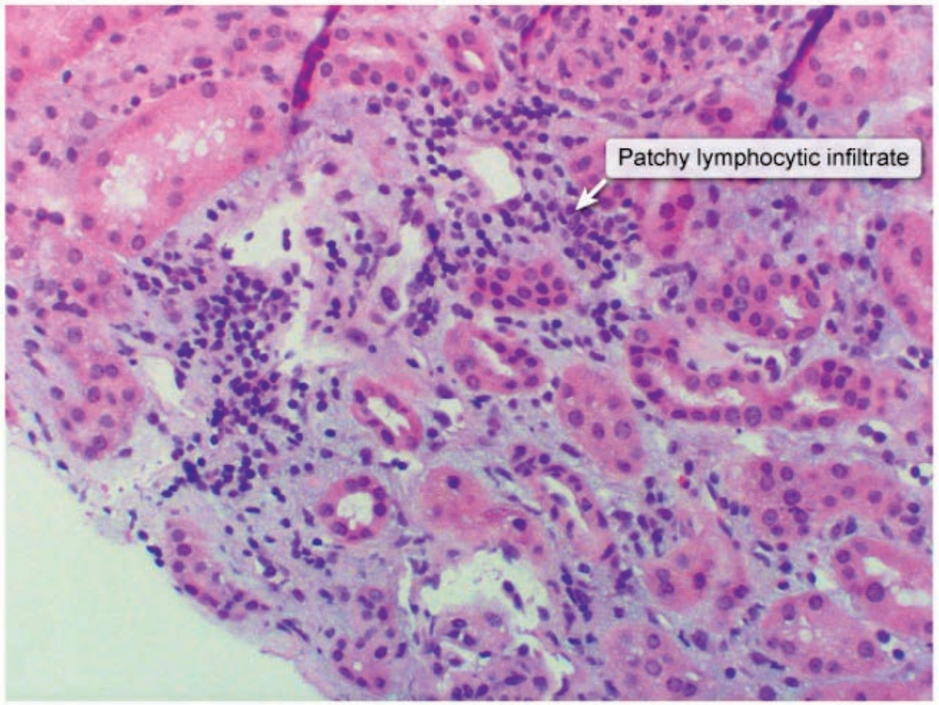
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findings	◦ ↑ Serum creatinine

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Acute postinfectious glomerulonephritis



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A 41-year-old woman is being evaluated for peripheral edema. The patient has gained 6.8 kg (15 lb) over the past 8 weeks. Her urine is "frothy." She has no other medical problems and takes no medications. The patient does not use tobacco, alcohol, or illicit drugs. Blood pressure is 140/90 mm Hg and pulse is 80/min. Examination shows generalized edema. Heart sounds are normal. The abdomen is soft and nontender. Serum creatinine is 1.1 mg/dL. Urinalysis shows 4+ protein, 0-3 leukocytes/hpf, and oval fat bodies. Serum contains IgG4 antibodies to the phospholipase A2 receptor (PLA2R), a transmembrane protein abundant on podocytes. Which of the following is the most likely diagnosis?

- A. Focal segmental glomerulosclerosis
- B. Membranous nephropathy
- C. Minimal change disease
- D. Mixed cryoglobulinemia
- E. Multiple myeloma

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- A. Focal segmental glomerulosclerosis (13%)
- ✓ B. Membranous nephropathy (73%)
- C. Minimal change disease (8%)
- D. Mixed cryoglobulinemia (2%)
- E. Multiple myeloma (1%)

Correct | 73% Answered correctly | 04 secs Time Spent | 2023 Version

Explanation

This patient with weight gain and edema with 4+ protein and oval fat bodies on urinalysis has **nephrotic syndrome**. The presence of **phospholipase A2 receptor** (PLA2R) antibodies suggests a diagnosis of membranous nephropathy. Antibodies against PLA2R, primarily IgG4, can lead to immune deposition in the glomerulus and are thought to be a major factor in the pathogenesis of primary (idiopathic) **membranous nephropathy**, a common cause of nephrotic syndrome in adults.

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Anti-PLA2R antibodies are highly specific for membranous nephropathy; positive titers effectively rule out other causes of nephrotic syndrome (eg, focal segmental glomerulosclerosis) and may eliminate the need for invasive renal biopsy. In addition, **titers correlate with disease activity**, and serial measurements can be used to determine the efficacy of immunosuppressive therapy.

(Choice A) Focal segmental glomerulosclerosis causes nephrotic syndrome but is caused by direct (eg, cytotoxic drugs) or indirect (eg, glomerular hyperfiltration) podocyte injury. It is not associated with anti-PLA2R antibodies.

(Choice C) Minimal change disease may be due to abnormal T-cell production of a glomerular permeability factor that affects the glomerular capillary wall, leading to fusion of the foot processes and marked proteinuria. There has been no association with anti-PLA2R antibodies.

(Choice D) Mixed cryoglobulinemia is associated with IgM deposition in the glomerulus, leading to basement membrane thickening and cellular proliferation. Renal disease typically presents as membranoproliferative glomerulonephritis with hematuria and red blood cell casts. It is most common in patients with chronic hepatitis C infection.

(Choice E) Renal disease in multiple myeloma is due to deposition of light chains (ie, cast nephropathy) and is not associated with anti-PLA2R antibodies.

Educational objective:
Primary (idiopathic) membranous nephropathy is associated with IgG4 antibodies to the phospholipase A2 receptor, which might play a role in development of the disease. Antibody titers are useful for diagnosis and

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(Choice E) Renal disease in multiple myeloma is due to deposition of light chains (ie, cast nephropathy) and is not associated with anti-PLA2R antibodies.

Educational objective:
Primary (idiopathic) membranous nephropathy is associated with IgG4 antibodies to the phospholipase A2 receptor, which might play a role in development of the disease. Antibody titers are useful for diagnosis and correlate with disease activity.

References

- M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy

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A 48-year-old woman is evaluated for postcoital bleeding and vaginal discharge. Pelvic examination shows a friable mass at the cervix that bleeds easily on touch. Cervical biopsy confirms invasive squamous cell cancer confined to the cervix and uterus. Lymph node metastases are not seen. A radical hysterectomy is performed during which the right ureter is accidentally injured but then repaired. Imaging studies performed after the surgery show a partial obstruction of the right ureter with mild dilation of the proximal collecting system. Which of the following changes are most likely to be seen in the right kidney?

	Glomerular Filtration Rate	Filtration Fraction
○ A.	No change	↑
○ B.	↑	↓
○ C.	↓	↑
○ D.	↓	No change
○ E.	↓	↓

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A 48-year-old woman is evaluated for postcoital bleeding and vaginal discharge. Pelvic examination shows a friable mass at the cervix that bleeds easily on touch. Cervical biopsy confirms invasive squamous cell cancer confined to the cervix and uterus. Lymph node metastases are not seen. A radical hysterectomy is performed during which the right ureter is accidentally injured but then repaired. Imaging studies performed after the surgery show a partial obstruction of the right ureter with mild dilation of the proximal collecting system. Which of the following changes are most likely to be seen in the right kidney?

	Glomerular Filtration Rate	Filtration Fraction	
A.	No change	↑	(5%)
✗ B.	↑	↓	(5%)
C.	↓	↑	(9%)
D.	↓	No change	(12%)
✓ E.	↓	↓	(67%)

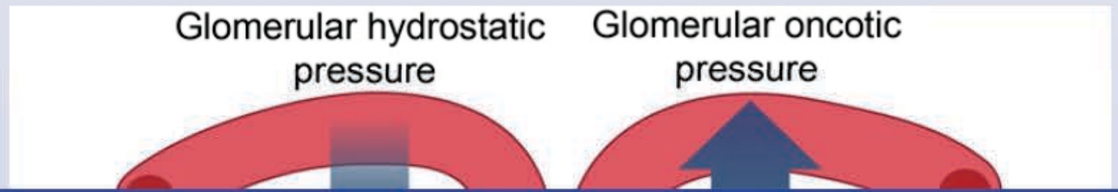
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Correct answer
E

67%
Answered correctly

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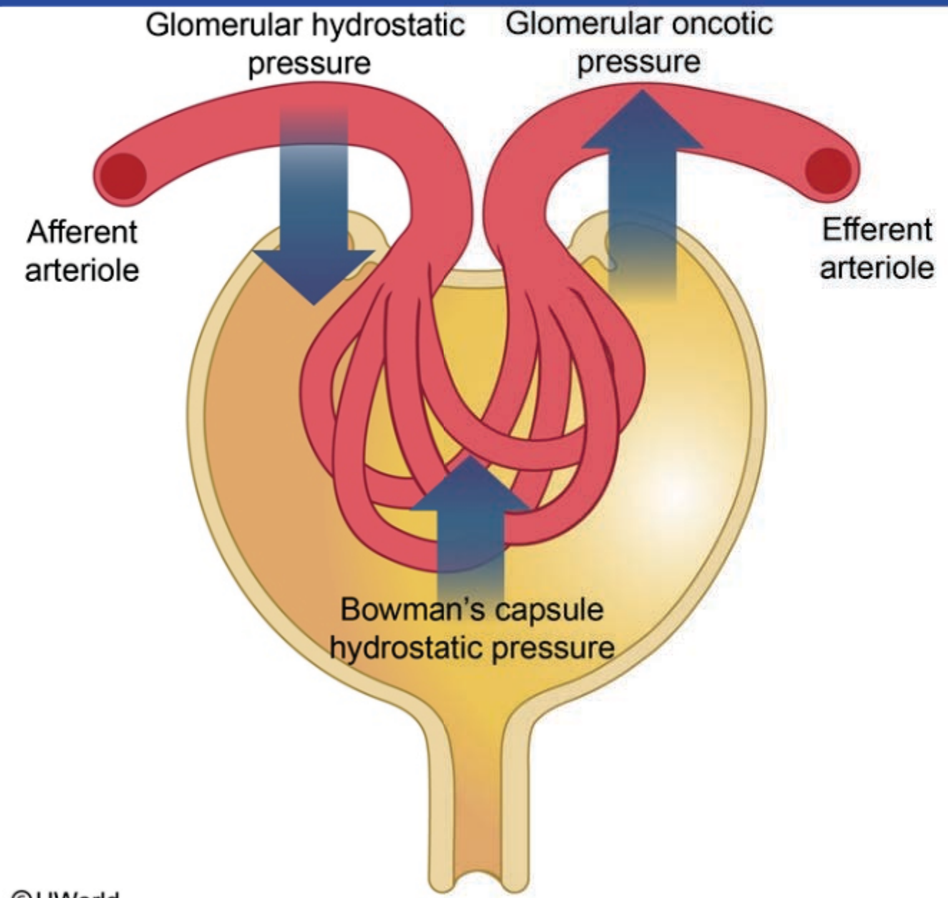
Explanation



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A. No change ↑ (5%)

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The glomerular filtration rate (GFR) depends on the interplay of hydrostatic and oncotic pressures in the glomerular capillaries and Bowman's space. The GFR increases with higher glomerular hydrostatic pressure and decreases with increasing Bowman's capsule hydrostatic pressure or higher glomerular capillary oncotic pressure. Acute **ureteral obstruction** increases hydrostatic pressure proximal to the constriction. This pressure rise is transmitted back to the Bowman's space, resulting in **decreased GFR**.

The filtration fraction (FF) is the portion of the renal plasma flow (RPF) that is filtered from the glomerular capillaries into Bowman's space (ie, the GFR:RPF ratio). With acute ureteral obstruction (first 12 hours), the RPF may transiently increase; however, with time, efferent arteriolar constriction (in response to reduced GFR) will decrease RPF. Even at later stages, though, the GFR remains depressed to a greater extent than the RPF, resulting in **reduced FF**.

Educational objective:
Acute ureteral constriction or obstruction decreases the glomerular filtration rate and filtration fraction.

References

- Renal hemodynamics in acute unilateral ureteral obstruction: contribution of endothelium-derived relaxing factor.

Physiology	Renal, Urinary Systems & Electrolytes	GFR
Subject	System	Topic

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A 58-year-old man comes to the emergency department due to generalized weakness, anorexia, and nausea for the past several weeks. He also reports lower extremity swelling but has had no dyspnea or chest pain. The patient was diagnosed with hypertension several years ago but did not follow up and takes no medications. Blood pressure is 182/100 mm Hg and pulse is 84/min. Physical examination shows pitting edema of the bilateral lower extremities. Laboratory studies reveal elevated serum creatinine and blood urea nitrogen levels. During evaluation of renal dysfunction, total urinary creatinine is measured over a 24-hour period, and creatinine clearance is calculated using the serum and urine creatinine concentrations and urinary volume. Compared to the calculated creatinine clearance, this patient's true glomerular filtration rate is most likely to be:

- A. 20% higher
- B. 20% lower
- C. 90% higher
- D. 90% lower
- E. Equal

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- A. 20% higher (19%)
- ✓ B. 20% lower (65%)
- C. 90% higher (1%)
- D. 90% lower (4%)
- E. Equal (10%)

Correct

65%
Answered correctly

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Explanation

This patient with elevated creatinine and blood urea nitrogen levels has symptoms of uremia (eg, weakness, nausea, anorexia) due to kidney disease, most likely from chronic uncontrolled hypertension.

Kidney filtration function is reflected by the **glomerular filtration rate (GFR)**, which is the sum of the filtration rates

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Explanation

This patient with elevated creatinine and blood urea nitrogen levels has symptoms of uremia (eg, weakness, nausea, anorexia) due to kidney disease, most likely from chronic uncontrolled hypertension.

Kidney filtration function is reflected by the **glomerular filtration rate (GFR)**, which is the sum of the filtration rates of all the nephrons in the kidneys. Normal GFR ranges between 120 and 130 mL/min per 1.73 m^2 of body surface area, and can vary considerably based on age, sex, and body habitus. GFR is reduced in both chronic kidney disease (due to loss of functional nephrons) and acute kidney injury (eg, due to decreased renal perfusion).

The GFR can be directly measured using an **ideal filtration marker** that is **freely filtered** across the glomerulus and is **not metabolized, secreted, or reabsorbed** by the kidney tubules. However, this is time intensive and invasive and requires multiple blood draws. In addition, the substance previously used to perform these calculations, inulin, is no longer available in the United States.

Because of the limitations in directly measuring GFR, renal filtration function is more commonly estimated using **creatinine**, a waste product generated from the breakdown of creatine in the muscles. Creatinine is released from muscle at a relatively constant rate and is neither metabolized nor reabsorbed by the kidney. However, in addition to passive filtration, a portion of creatinine is **actively secreted** by the proximal tubules. Therefore, uncorrected creatinine clearance **overestimates the GFR by approximately 10%-20%**. Creatinine clearance has further limitations in patients with low muscle mass (eg, malnutrition, lower extremity amputation) or high- or low-protein diets.

(Choices A, C, D, and E) Creatinine clearance overestimates the GFR by 10%-20% due to the proximal tubular secretion of creatinine.

Educational objective:

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(Choices A, C, D, and E) Creatinine clearance overestimates the GFR by 10%-20% due to the proximal tubular secretion of creatinine.

Educational objective:
Glomerular filtration rate (GFR) can be assessed using an ideal filtration marker that is freely filtered across the glomerulus and is not metabolized, secreted, or reabsorbed by the kidney tubules. In common practice, GFR is estimated using creatinine clearance. However, creatinine is actively secreted by the proximal tubules, so uncorrected creatinine clearance overestimates the GFR by approximately 10%-20%.

Physiology	Renal, Urinary Systems & Electrolytes	Creatinine clearance
Subject	System	Topic

https://t.me/USMLEWorldStep1

An 80-year-old woman presents to the office for evaluation of progressively worsening urinary incontinence. The patient reports that she is leaking urine "all of the time" and is using the bathroom multiple times at night. She loses urine immediately after she has the urge to void and often cannot make it to the bathroom. The patient was recently diagnosed with mild cognitive impairment but maintains independence with the assistance of her husband. She has no other medical problems. Vital signs are normal. Pelvic examination shows vaginal atrophy but is otherwise normal. There is no leaking of urine with cough or Valsalva maneuver. Postvoid residual volume and urinalysis are normal. A medication with which of the following pharmacodynamic effects would be most helpful in treating this patient's urinary incontinence?

- A. Antagonism of alpha-1 adrenergic receptors
- B. Antagonism of beta-1 adrenergic receptors
- C. Antagonism of beta-3 adrenergic receptors
- D. Stimulation of beta-1 adrenergic receptors
- E. Stimulation of beta-3 adrenergic receptors
- F. Stimulation of muscarinic cholinergic receptors

Submit

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- A. Antagonism of alpha-1 adrenergic receptors (15%)
- ✗ B. Antagonism of beta-1 adrenergic receptors (4%)
- C. Antagonism of beta-3 adrenergic receptors (14%)
- D. Stimulation of beta-1 adrenergic receptors (6%)
- ✓ E. Stimulation of beta-3 adrenergic receptors (44%)
- F. Stimulation of muscarinic cholinergic receptors (15%)

Incorrect
Correct answer
E

44%
Answered correctly

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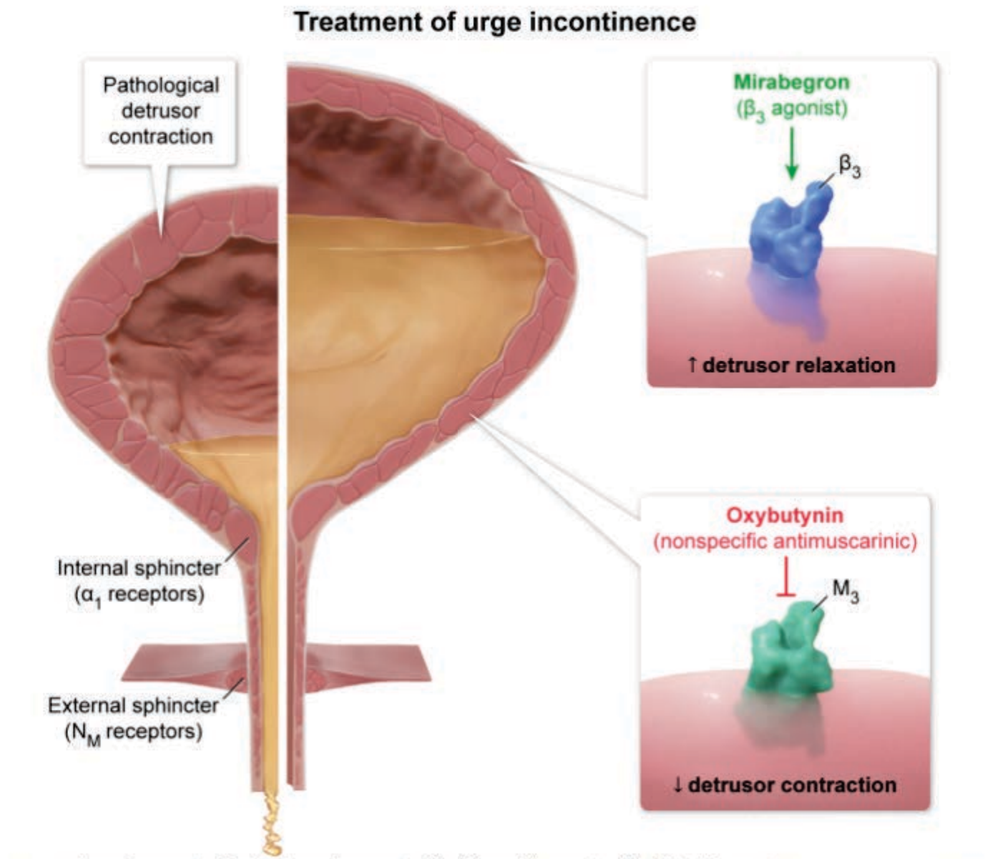
Explanation

Treatment of urge incontinence

https://t.me/USMLEWorldStep1

An 8 year-old woman presents to the office for evaluation of progressively worsening urinary incontinence. The
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The patient has **urgency incontinence** (or overactive bladder), which is caused by **uninhibited bladder contractions** (detrusor instability) that results in a sudden, **strong urge to void** followed immediately by loss of urine. Pharmacotherapy in these patients is aimed at either promoting detrusor relaxation (via beta-3 adrenoceptors) or inhibiting contraction (via muscarinic cholinergic receptors) with 2 main medication classes:

- **Beta-3 receptor agonists** (eg, mirabegron), which causes **detrusor smooth muscle relaxation**, allow increased urine storage and decrease incontinent episodes. Because they are selective receptor agonists, they are often better tolerated with fewer systemic adverse effects.
- **Antimuscarinics** (eg, oxybutynin), which block M_3 receptors at the bladder, prevent detrusor contractions. However, antimuscarinics often act on several types of muscarinic receptors and should be used with caution, especially in elderly patients and those with cognitive impairment due to medication adverse effects (eg, decreased cognition, blurred vision, drowsiness).

(Choice A) Alpha-1 blockers (eg, doxazosin, prazosin, terazosin) are used to treat benign prostatic hyperplasia (BPH) and hypertension. They relax the smooth muscle in arterial and venous walls, leading to decreased peripheral vascular resistance, and also relax the smooth muscle in the bladder neck and prostate, leading to decreased urinary obstruction in patients with BPH.

(Choices B and D) Beta-1 adrenergic receptors are found in cardiac tissue and on renal juxtaglomerular cells. Selective beta-1 blockers (eg, metoprolol) decrease heart rate and contractility and block catecholamine-induced renin release by the kidney.

(Choice C) In contrast to beta-3 adrenergic receptor agonists, antagonists would cause increased bladder spasms (ie, contractions) and increased urine loss.

(Choice F) Muscarinic receptor activation leads to contractions of the bladder musculature and promotes bladder emptying. Cholinergic agonists (eg, bethanechol) are used to treat urinary retention or neurogenic bladder by strengthening muscular contractions. These medications would worsen this patient's symptoms.

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Educational objective:
Urgency incontinence, or overactive bladder, is caused by uninhibited bladder contractions (detrusor instability) that results in a sudden urge to void followed by an involuntary loss of urine. Treatment with beta-3 adrenergic receptor activation (eg, mirabegron) relaxes the detrusor muscle, promotes urine storage, and decreases incontinent episodes.

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A 68-year-old man comes to the office due to a weak urinary stream, hesitancy, and straining on micturition. These symptoms have been present for the past 2 years but have gradually become more severe and are beginning to affect his quality of life. The patient recently started noticing continuous urine leakage, nocturia, frequent urination, and urgency. He has no other medical problems and takes no medications. The patient does not use tobacco or alcohol. He is a business management consultant and motivational speaker. Vital signs are normal. BMI is 27 kg/m^2. The patient's kidneys are most likely to demonstrate which of the following findings?

- A. Glomerular sclerosis and hyalinosis
- B. Hyperplastic arteriolar changes
- C. Ischemic tubular necrosis
- D. Parenchymal pressure atrophy
- E. Tubular epithelial dysplasia

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- A. Glomerular sclerosis and hyalinosis (8%)
- ✗ B. Hyperplastic arteriolar changes (8%)
- C. Ischemic tubular necrosis (2%)
- ✓ D. Parenchymal pressure atrophy (73%)
- E. Tubular epithelial dysplasia (7%)

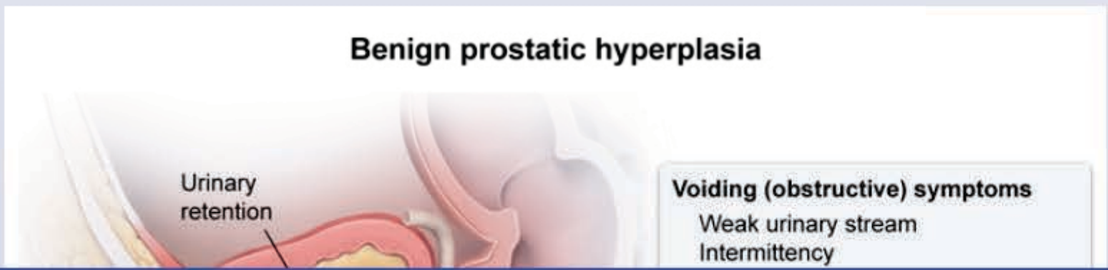
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Correct answer
D

73%
Answered correctly

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Explanation



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Incorrect
Correct answer

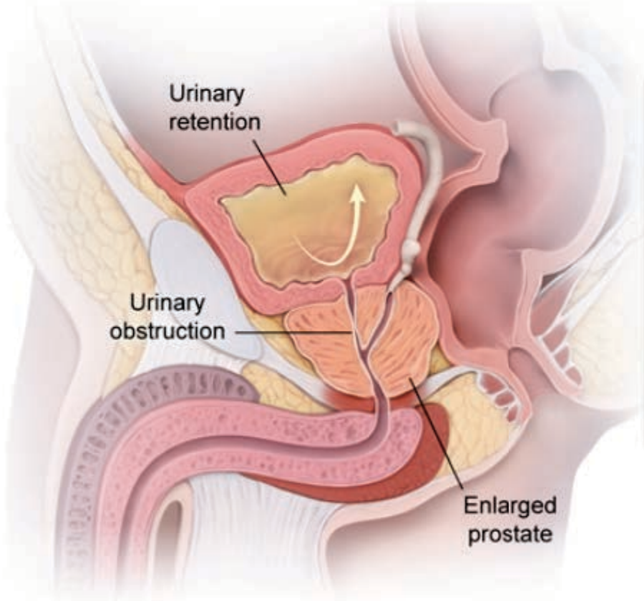
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Benign prostatic hyperplasia



Voiding (obstructive) symptoms
- Weak urinary stream
- Intermittency
- Incomplete emptying
- Hesitancy
- Straining to void

Storage (irritative, filling) symptoms
- Frequency
- Urgency
- Nocturia
- Incontinence

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This
BPH
prec
cont

As the prostate enlarges it impinges on the prostatic urethra, causing progressively worsening **bladder outlet**

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This patient has progressive lower urinary tract symptoms, likely due to **benign prostatic hyperplasia** (BPH). BPH is common in older men and is characterized by a combination of epithelial and stromal hyperplasia, predominantly in the periurethral and transition zones. On palpation, the prostate has a rubbery consistency, in contrast to prostate cancer, in which the gland is nodular and very firm.

As the prostate enlarges it impinges on the prostatic urethra, causing progressively worsening **bladder outlet obstruction**. This leads to problems voiding (eg, hesitancy, straining, weak urinary stream) and impaired urine storage (eg, daytime frequency, urgency, nocturia). As BPH progresses, incomplete bladder emptying leads to overflow incontinence (involuntary urine spillage from an overly full bladder). **Increased hydrostatic force** is needed to overcome the obstruction, causing hypertrophy of the bladder wall musculature and dilation of the ureters, renal pelvis, and calyces (**hydronephrosis**). If left untreated, urinary reflux can lead to significant pressure-induced **parenchymal atrophy** with scarring and eventual **chronic kidney disease**.

(Choice A) Glomerular sclerosis and hyalinosis are typical of diabetic nephrosclerosis and focal segmental glomerulosclerosis (FSGS). Diabetes can cause autonomic neuropathy with overflow incontinence, but it is rare and typically occurs in poorly controlled chronic diabetes. FSGS does not cause lower urinary tract symptoms.

(Choice B) Hyperplastic arteriolar changes are seen in severe (malignant) hypertension. Hypertension does not cause lower urinary tract symptoms. Additionally, this patient does not have a history of high blood pressure or symptoms associated with malignant hypertension (eg, headache, blurred vision).

(Choice C) Ischemic tubular necrosis results from decreased renal perfusion (eg, sepsis, hemorrhage, heart failure). Patients develop oliguria, azotemia (elevated blood levels of nitrogenous wastes), elevated serum creatinine, and electrolyte disturbances.

(Choice E) Epithelial dysplasia (eg, alterations in cell shape and size, nuclei size, and staining) is considered a precursor of malignancy. BPH does not predispose to renal tubular dysplasia or prostate cancer.

Educational objective:

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contrast to prostate cancer, in which the gland is nodular and very firm.

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Educational objective:
Benign prostatic hyperplasia leads to progressive bladder outlet obstruction. Over time, increased urinary pressures can cause hydronephrosis and renal parenchymal atrophy with scarring. This can progress to chronic kidney disease.

https://t.me/USMLEWorldStep1

A 76-year-old man comes to the hospital due to acute, bright red blood from the rectum. The patient had 3 large bloody bowel movements this morning, and he has felt light-headed and dizzy since. He has a history of sigmoid diverticulosis and, 2 years ago, had a similar episode of bleeding that resolved spontaneously. Temperature is 36.9 C (98.4 F), blood pressure is 90/50 mm Hg, and pulse is 110/min. Examination shows mild lethargy and delayed capillary refill. Abdominal examination shows no abnormalities. Which of the following physiologic changes in kidney function would be most likely in this patient?

- A. Decreased chloride reabsorption
- B. Decreased sodium reabsorption
- C. Decreased urine osmolality
- D. Increased renal blood flow
- E. Increased tubular hydrostatic pressure
- F. Increased urea reabsorption

Submit

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- A. Decreased chloride reabsorption (4%)
- ✗ B. Decreased sodium reabsorption (6%)
- C. Decreased urine osmolality (13%)
- D. Increased renal blood flow (6%)
- E. Increased tubular hydrostatic pressure (9%)
- ✓ F. Increased urea reabsorption (58%)

Incorrect
Correct answer
F

58%
Answered correctly

03 secs
Time Spent

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Explanation

This patient has acute gastrointestinal hemorrhage resulting in **hypovolemic shock**. Clinically significant hypovolemia can occur due to acute blood loss, third-spacing (eg, pancreatitis, vasodilation in sepsis), or renal or gastrointestinal losses (eg, excessive diuresis, diarrhea). Signs of hypovolemia include dry skin with decreased turgor, dry mucous membranes, decreased urine output, and orthostatic hypotension.

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Changes in blood volume or osmolality are detected by sensors in the carotid, hypothalamus, atria, and kidneys and result in activation of multiple compensatory mechanisms:

- Activation of the renin-angiotensin-aldosterone system results in systemic vasoconstriction and increased aldosterone release. Aldosterone increases **sodium reabsorption** and potassium excretion in the distal tubule and collecting duct.
- The hypothalamus stimulates thirst and increases the secretion of **antidiuretic hormone** (via the posterior pituitary), which promotes water reabsorption in the collecting duct and increases systemic vasoconstriction.
- Sympathetic activity increases renal tubular sodium reabsorption, cardiac output, and systemic vasoconstriction.

The net effect is a rapid increase in blood pressure that helps maintain tissue perfusion, while the kidney begins the slower process of restoring circulatory volume by increasing sodium, urea, and water reabsorption. **Increased urea reabsorption** is mediated by antidiuretic hormone, which increases urea permeability in the inner medullary collecting ducts. The increase in urea reabsorption accentuates the medullary concentration gradient, promoting maximal free water retention. These actions typically result in an elevated serum urea level and blood urea nitrogen/creatinine ratio (typically >20:1). Urine parameters typically show **low urine sodium concentration** (<20 mEq/L), low fractional excretion of sodium, **high urine osmolality** (>450 mOsmol/kg), and elevated urine potassium.

(Choices A, B, and C) Hypovolemia leads to increased renal salt reabsorption and elevated urine osmolality due to high serum levels of aldosterone and antidiuretic hormone.

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tubule and collecting duct.

- The hypothalamus stimulates thirst and increases the secretion of **antidiuretic hormone** (via the posterior pituitary), which promotes water reabsorption in the collecting duct and increases systemic vasoconstriction.
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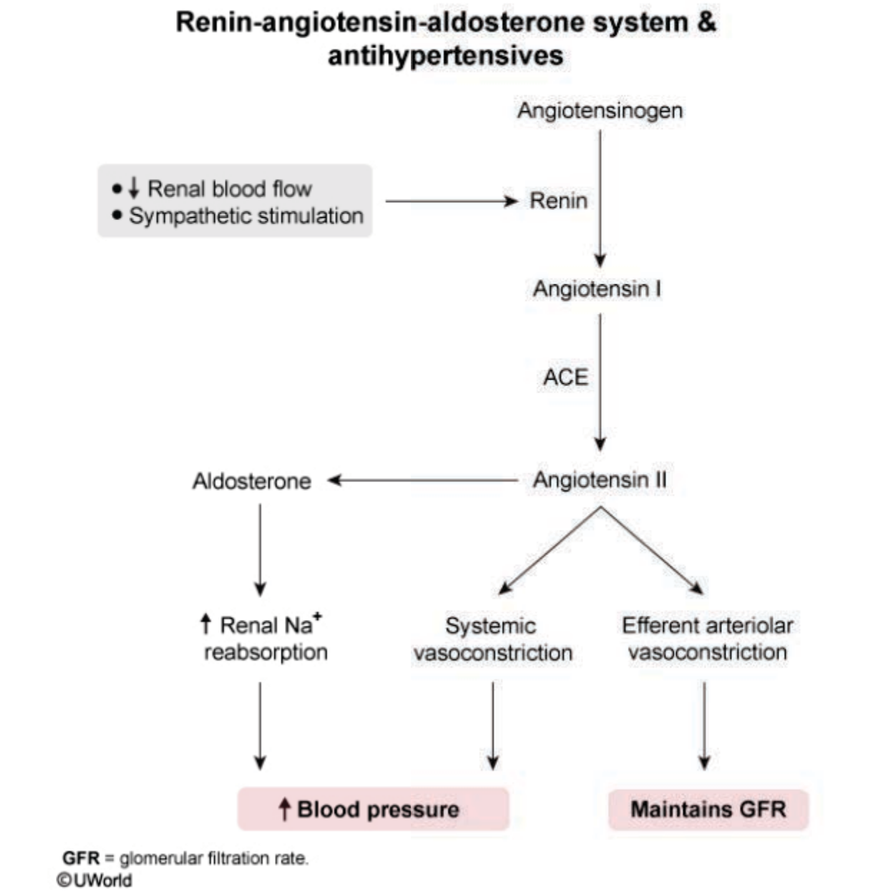
(Choices A, B, and C) Hypovolemia leads to increased renal salt reabsorption and elevated urine osmolality due to high serum levels of aldosterone and antidiuretic hormone.

(Choices D and E) Renal blood flow and tubular hydrostatic pressure are decreased, not increased, in patients with hypovolemia. Although activation of the renin-angiotensin-aldosterone system increases renal blood flow and tubular hydrostatic pressure in an attempt to maintain the glomerular filtration rate, these would still be lower in this patient than in a healthy patient.

Educational objective:
Compensatory mechanisms for hypovolemia include activation of the renin-angiotensin-aldosterone system and increased antidiuretic hormone release. This results in increased renal sodium, chloride, water, and urea reabsorption with increased potassium excretion.

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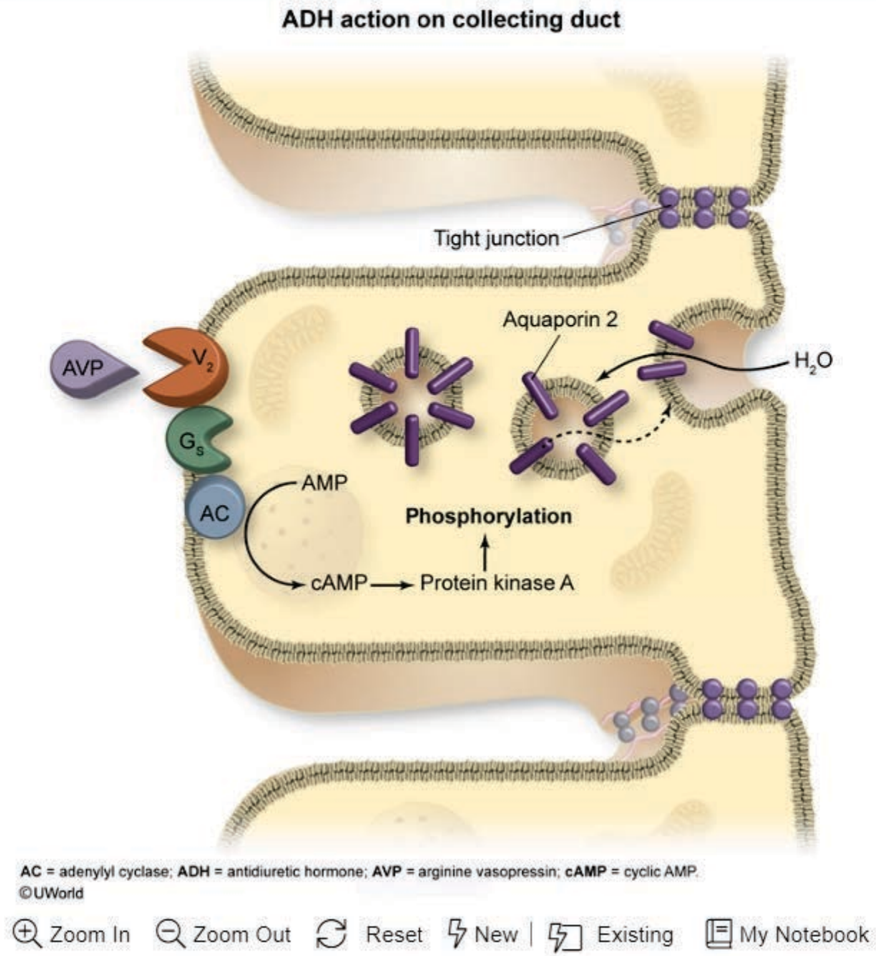
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collecting ducts. The increase in urea reabsorption accentuates the medullary concentration gradient, promoting maximal free water retention. These actions typically result in an elevated serum urea level and blood urea

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1. Increased urea reabsorption (56%)

Exhibit Display



AC = adenylyl cyclase; **ADH** = antidiuretic hormone; **AVP** = arginine vasopressin; **cAMP** = cyclic AMP.
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collecting ducts. The increase in urea reabsorption accentuates the medullary concentration gradient, promoting maximal free water retention. These actions typically result in an elevated serum urea level and blood urea

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A 51-year-old man comes to the emergency department with sudden-onset, sharp, left flank pain; nausea; and vomiting. He has had no dysuria or hematuria. The patient has no past medical conditions and takes no daily medications. He does not use tobacco, alcohol, or illicit drugs. Temperature is normal. On examination, the patient appears to be in severe pain and cannot find a comfortable position on the bed. There is no abdominal rigidity or rebound, and no masses are palpable. Cardiopulmonary examination is normal. There is no peripheral edema. Imaging shows a 1-cm calculus in the left proximal ureter at the level of the L3 vertebra; the renal pelvis and proximal ureter are dilated, as shown in the exhibit. Which of the following is most likely increased in this patient's left kidney?

- A. Bowman space oncotic pressure
- B. Glomerular filtration
- C. Intraglomerular capillary hydrostatic pressure
- D. Tubular hydrostatic pressure
- E. Tubular oncotic pressure

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A 51-year-old man comes to the emergency department with sudden-onset, sharp, left flank pain, nausea, and vom
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Exhibit Display



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A 51-year-old man comes to the emergency department with sudden-onset, sharp, left flank pain; nausea; and vomiting. He has had no dysuria or hematuria. The patient has no past medical conditions and takes no daily medications. He does not use tobacco, alcohol, or illicit drugs. Temperature is normal. On examination, the patient appears to be in severe pain and cannot find a comfortable position on the bed. There is no abdominal rigidity or rebound, and no masses are palpable. Cardiopulmonary examination is normal. There is no peripheral edema. Imaging shows a 1-cm calculus in the left proximal ureter at the level of the L3 vertebra; the renal pelvis and proximal ureter are dilated, as shown in the exhibit. Which of the following is most likely increased in this patient's left kidney?

- A. Bowman space oncotic pressure (3%)
- B. Glomerular filtration (3%)
- C. Intraglomerular capillary hydrostatic pressure (11%)
- ✓ D. Tubular hydrostatic pressure (79%)
- E. Tubular oncotic pressure (3%)

Correct

79% Answered correctly

38 secs Time Spent

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Explanation

The glomerular filtration rate depends on the permeability of the capillary wall and the net ultrafiltration pressure. Net ultrafiltration pressure is a result of pressure gradients formed by Starling forces:

- **The hydrostatic pressure gradient** is the difference between the hydrostatic pressure in the intraglomerular

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The glomerular filtration rate depends on the permeability of the capillary wall and the net ultrafiltration pressure. Net ultrafiltration pressure is a result of pressure gradients formed by Starling forces:

- **The hydrostatic pressure gradient** is the difference between the hydrostatic pressure in the intraglomerular capillaries and the Bowman space. Typically, the hydrostatic pressure in the glomerular capillaries is markedly greater than the pressure in the Bowman space, favoring filtration.
- **The oncotic pressure gradient** is the difference between the oncotic pressure in the intraglomerular capillaries and the Bowman space. Oncotic pressure is chiefly driven by large plasma proteins (eg, albumin), which do not freely filter across the glomerular capillary basement membrane due to both a size and charge barrier. Therefore, the oncotic pressure is negligible within the Bowman space, favoring absorption of fluid into the glomerular capillaries.

This patient has a kidney stone in the left ureter; the hydroureter and hydronephrosis suggest acute **urinary tract obstruction**. The resultant reflux of urine backward into the relatively noncompliant renal tubules results in **increased renal tubular hydrostatic pressure**. As the intraglomerular capillary hydrostatic pressure is unchanged, this results in a decreased hydrostatic pressure gradient leading to a reduction in glomerular filtration **(Choices B and C)**.

(Choices A and E) Oncotic pressure in the Bowman space is negligible unless glomerular disease (eg, minimal change disease, diabetic nephropathy) allows proteins to leak into the Bowman space. The renal tubules are contiguous with the Bowman space and therefore also have negligible oncotic pressure. Acute urinary tract obstruction would not affect protein filtration at the glomerulus; therefore, the oncotic pressure in these regions remains essentially unchanged.

Educational objective:
Urinary tract obstruction causes reflux of urine into the renal tubules and increased tubular hydrostatic pressure. The intraglomerular capillary hydrostatic pressure is unchanged, resulting in a decreased hydrostatic pressure gradient across the glomerular capillary wall and a reduction in glomerular filtration. Oncotic pressure is

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capillaries and the Bowman space. Typically, the hydrostatic pressure in the glomerular capillaries is markedly greater than the pressure in the Bowman space, favoring filtration.

- **The oncotic pressure gradient** is the difference between the oncotic pressure in the intraglomerular capillaries and the Bowman space. Oncotic pressure is chiefly driven by large plasma proteins (eg, albumin), which do not freely filter across the glomerular capillary basement membrane due to both a size and charge barrier. Therefore, the oncotic pressure is negligible within the Bowman space, favoring absorption of fluid into the glomerular capillaries.

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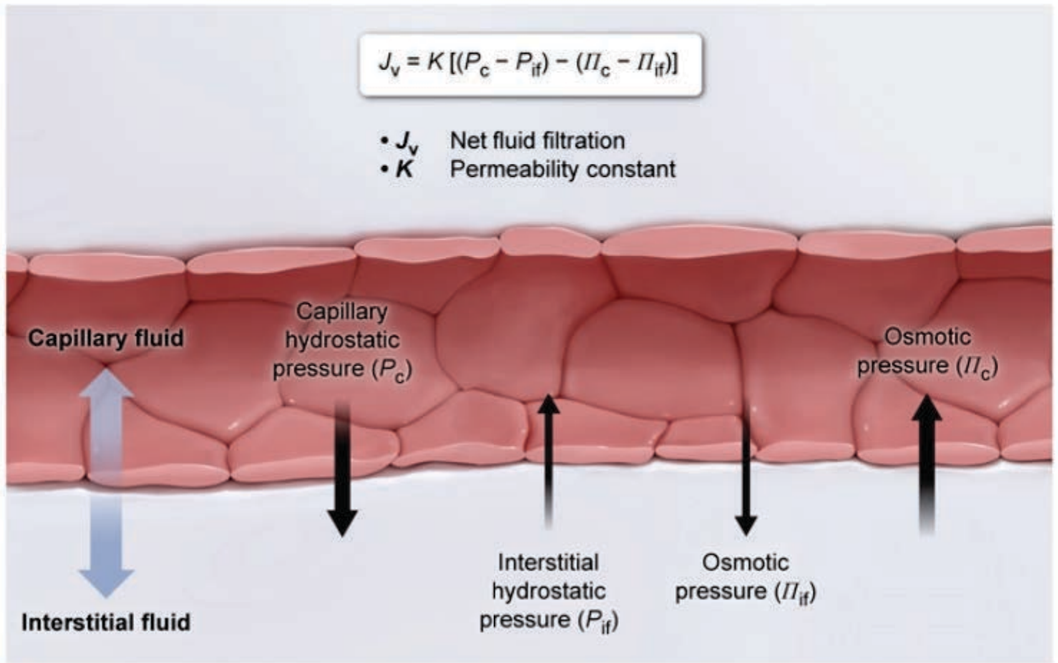
Educational objective:
Urinary tract obstruction causes reflux of urine into the renal tubules and increased tubular hydrostatic pressure. The intraglomerular capillary hydrostatic pressure is unchanged, resulting in a decreased hydrostatic pressure gradient across the glomerular capillary wall and a reduction in glomerular filtration. Oncotic pressure is maintained by large plasma proteins which are not filtered across the glomerular capillary basement membrane; it is unaffected by a urinary tract obstruction.

References

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Starling equation & capillary fluid exchange



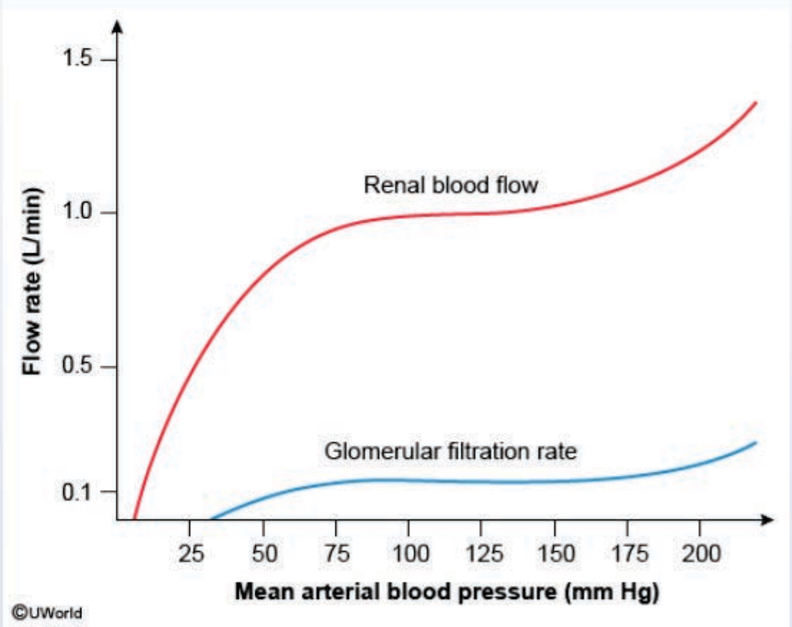
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Educational objective:

Physiologists are investigating renal autoregulatory mechanisms in an animal species that closely mimics human physiology. During one of their experiments, renal blood flow and glomerular filtration rate are measured in an anesthetized animal in response to changes in mean arterial pressure. The data they obtain is shown on the graph below.



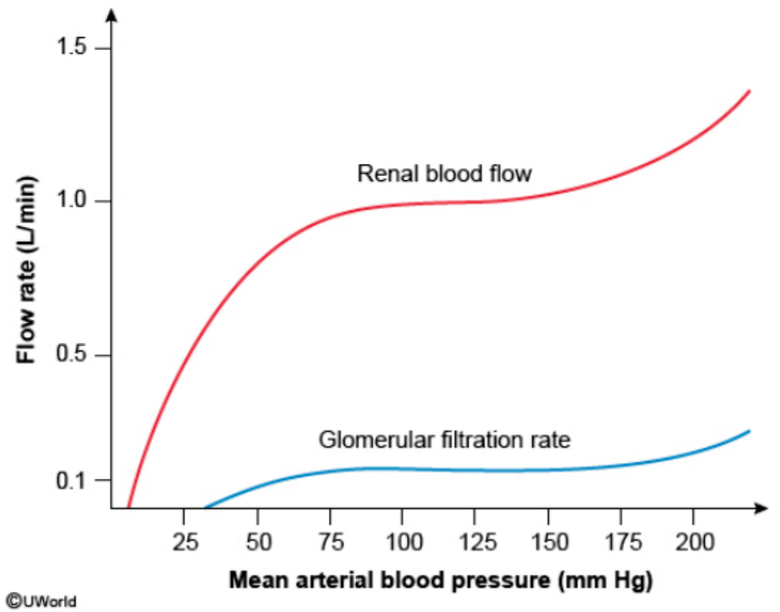
Assuming a hematocrit of 0.50, what is the best estimate of the filtration fraction when the mean arterial pressure is 120 mm Hg?

- A. 0.1
- B. 0.2
- C. 0.4

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Physiologists are investigating renal autoregulatory mechanisms in an animal species that closely mimics human
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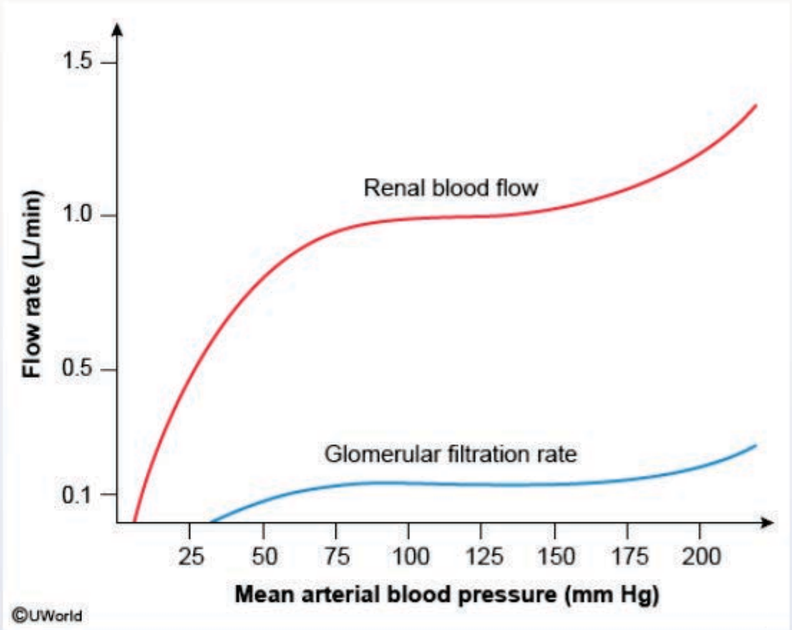
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C. 0.4

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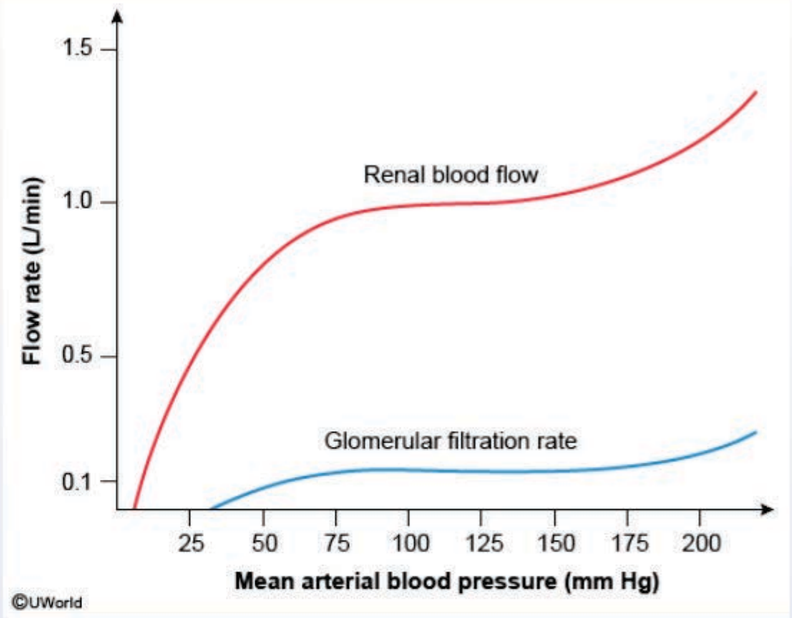
anesthetized animal in response to changes in mean arterial pressure. The data they obtain is shown on the graph below.



Assuming a hematocrit of 0.50, what is the best estimate of the filtration fraction when the mean arterial pressure is 120 mm Hg?

- A. 0.1
- B. 0.2
- C. 0.4
- D. 0.5
- E. 0.9

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Assuming a hematocrit of 0.50, what is the best estimate of the filtration fraction when the mean arterial pressure is 120 mm Hg?

- A. 0.1 (31%)
- ✓ B. 0.2 (47%)
- ✗ C. 0.4 (5%)
- D. 0.5 (11%)
- E. 0.9 (3%)

Incorrect
Correct answer
B

47%
Answered correctly

13 secs
Time Spent

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Explanation

The **filtration fraction (FF)** is the fraction of **plasma** flowing through the glomeruli that is filtered across the glomerular capillaries into Bowman's space. It can be thought of as the ratio between the glomerular filtration rate (GFR) and renal plasma flow (RPF):

FF = GFR/RPF

RPF is used to calculate FF rather than renal blood flow (RBF) because RBF includes the volume of the blood that is occupied by erythrocytes, a volume unavailable for filtration across the glomerular capillaries. The RPF quantifies the volume of plasma that is able to pass through the glomerular capillaries more accurately and can be calculated from the RBF using the following equation:

RPF = RBF * (1 - Hematocrit)

In this case, at a mean arterial pressure of 120 mm Hg, the experimental animal has a RBF of 1.0 L/min and a GFR of 0.1 L/min. Because the hematocrit is 0.5, this gives:

RPF = (1.0 L/min) * (1 - 0.5) = 0.5 L/min

Therefore, FF = (0.1 L/min) / (0.5 L/min) = 0.2.

Educational objective:
The filtration fraction is the fraction of plasma flowing through the glomeruli that is filtered across the glomerular capillaries into Bowman's space (FF = GFR/RPF). Renal plasma flow can be determined from renal blood flow by multiplying the renal blood flow by (1 – Hematocrit).

Physiology	Renal, Urinary Systems & Electrolytes	Nephron structure & physiology
Subject	System	Topic

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A 45-year-old man comes to the emergency department due to urinary incontinence. He was diagnosed with multiple sclerosis a year ago after he developed transient acute vision loss in his right eye. A few weeks ago, he began having difficulty with his balance and had several episodes of urinary incontinence. The patient's walking has improved since, but he continues to urinate involuntarily. He has noticed increasing urinary frequency and cannot control the urge to urinate. His vital signs are normal. On examination, the patient has mild spastic paraparesis with increased reflexes in the lower extremities; bilateral Babinski sign; and a thoracic sensory level to pain, temperature, and vibration. An MRI of the spine reveals a new demyelinating lesion in the mid-thoracic spinal cord. Which of the following abnormalities will most likely be found on this patient's urodynamic studies?

- A. Bladder hypertonia
- B. Delayed bladder emptying
- C. Elevated urethral pressure
- D. Large residual volume of urine
- E. Reduced urine flow

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- ✓ A. Bladder hypertonia (63%)
- ✗ B. Delayed bladder emptying (6%)
- C. Elevated urethral pressure (4%)
- D. Large residual volume of urine (23%)
- E. Reduced urine flow (2%)

Incorrect
Correct answer
A

63%
Answered correctly

03 secs
Time Spent

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Explanation

This patient has urinary frequency and urge incontinence in the setting of an overactive or **spastic bladder** due to the presence of an **upper motor neuron lesion** in the spinal cord. Patients with **multiple sclerosis** often develop a spastic bladder a few weeks after developing an acute lesion of the spinal cord. **Urodynamic studies** show little or no residual urine after emptying as bladder contractility is normal but distensibility is poor. The **bladder does**

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This patient has urinary frequency and urge incontinence in the setting of an overactive or **spastic bladder** due to the presence of an **upper motor neuron lesion** in the spinal cord. Patients with **multiple sclerosis** often develop a spastic bladder a few weeks after developing an acute lesion of the spinal cord. **Urodynamic studies** show little or no residual urine after emptying as bladder contractility is normal but distensibility is poor. The **bladder does not distend/relax** properly due to loss of descending inhibitory control from the upper motor neuron.

(Choice B) This patient will have premature, as opposed to delayed, emptying due to his bladder overactivity. Delayed bladder emptying is more likely to occur in patients with diminished bladder tone.

(Choices C and E) Reduced urine flow and elevated urethral pressure indicate a mechanical obstruction (eg, enlarged prostate, urethral stricture) along the urinary tract.

(Choice D) Flaccid bladder typically occurs in the setting of lower motor neuron lesions (eg, cauda equina syndrome). A patient with a flaccid bladder will have a large residual volume of urine after attempted emptying and will typically experience urinary incontinence at the end of the day (pressure from a full bladder becomes greater than urinary sphincter pressure). In contrast, a patient with a spastic bladder will have frequent episodes of urinary incontinence throughout the day due to urgency.

Educational objective:
Patients with multiple sclerosis often develop a spastic bladder a few weeks after developing an acute lesion of the spinal cord. These patients present clinically with increased urinary frequency and urge incontinence. Urodynamic studies show the presence of bladder hypertonia.

References

- The neurogenic bladder in multiple sclerosis: review of the literature and proposal of management guidelines.
- The epidemiology and pathophysiology of neurogenic bladder.

Pathophysiology | Renal, Urinary Systems & Electrolytes | Urinary incontinence

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A 36-year-old woman comes to the office due to frequent urination since an exacerbation of multiple sclerosis 2 months ago. Most of her symptoms, including dizziness, leg weakness, and numbness, have improved with corticosteroid treatment. However, she has continued difficulty holding urine, and on several occasions has passed a small amount of urine while trying to reach the bathroom. She has no urine leakage during coughing or sneezing. The patient has no other medical problems. Her abdomen is soft and nontender. Neurological examination shows hyperreflexia and increased tone in the lower extremities. Her postvoid residual volume is low.

Glucose, serum	160 mg/dL
Urinalysis	
Blood	negative
Leukocyte esterase	negative
Bacteria	none
White blood cells	3-4/HPF

Which of the following is the most likely explanation for her urinary symptoms?

- A. Detrusor muscle weakness
- B. Hyperglycemia-induced osmotic diuresis
- C. Low-grade cystitis causing bladder irritation
- D. Pelvic floor laxity and urethral sphincter dysfunction
- E. Uninhibited bladder contraction

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Glucose, serum	160 mg/dL
Urinalysis	
Blood	negative
Leukocyte esterase	negative
Bacteria	none
White blood cells	3-4/HPF

Which of the following is the most likely explanation for her urinary symptoms?

- ✗ A. Detrusor muscle weakness (11%)
- B. Hyperglycemia-induced osmotic diuresis (8%)
- C. Low-grade cystitis causing bladder irritation (4%)
- D. Pelvic floor laxity and urethral sphincter dysfunction (13%)
- ✓ E. Uninhibited bladder contraction (62%)

Incorrect
Correct answer
E

62%
Answered correctly

04 secs
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Explanation

Differential diagnosis of urinary incontinence		
	Etiology	**Symptoms**
Stress	• ↓ Urethral sphincter tone • Urethral hypermobility	• Leakage with coughing, sneezing, lifting
Urge	• Detrusor overactivity	• Sudden, overwhelming urge to urinate
Overflow	• Impaired detrusor contractility • Bladder outlet obstruction	• Incomplete emptying & persistent involuntary dribbling

This patient's presentation is consistent with **urge incontinence**, which is due to detrusor overactivity causing a sudden and/or frequent urge to urinate and empty the bladder. The micturition reflex is an autonomic spinal reflex mediated by both sensory and motor fibers from nerve centers at the S2-S4 levels. Parasympathetic stimulation causes detrusor muscle contraction and internal urethral sphincter relaxation. Sympathetic fibers cause internal sphincter contraction and also help with sensing a full bladder.

Multiple sclerosis (MS) is likely an autoimmune disease that causes varying degrees of demyelination, inflammation, and gliosis in the central nervous system (eg, optic nerves, spinal cord, brainstem, periventricular white matter, and cerebellum). Regions in the pons and cerebral cortex partially inhibit the micturition reflex and also regulate contraction/relaxation of the external urethral sphincter. Spinal cord lesions above the sacral region cause a loss of higher center control of micturition and lead to detrusor hyperreflexia and urge incontinence. Patients typically develop a frequent urge to urinate and pass a small amount of urine. As the disease progresses, the bladder can become atonic and dilated leading to overflow incontinence.

(Choice A) Overflow incontinence can be due to impaired detrusor contractility or bladder outlet obstruction (eg, tumor obstructing urethra). Patients usually develop involuntary and continuous urinary leakage when the bladder

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inflammation, and gliosis in the central nervous system (eg, optic nerves, spinal cord, brainstem, periventricular white matter, and cerebellum). Regions in the pons and cerebral cortex partially inhibit the micturition reflex and also regulate contraction/relaxation of the external urethral sphincter. Spinal cord lesions above the sacral region cause a loss of higher center control of micturition and lead to detrusor hyperreflexia and urge incontinence. Patients typically develop a frequent urge to urinate and pass a small amount of urine. As the disease progresses, the bladder can become atonic and dilated leading to overflow incontinence.

(Choice A) Overflow incontinence can be due to impaired detrusor contractility or bladder outlet obstruction (eg, tumor obstructing urethra). Patients usually develop involuntary and continuous urinary leakage when the bladder is full and often have incomplete emptying. Post-void residual urine volume is usually high.

(Choice B) Osmotic diuresis due to hyperglycemia can occur in uncontrolled diabetes mellitus and causes polyuria. However, it more commonly occurs with blood sugar >250 mg/dL. This patient's blood sugar of 160 mg/dL and absence of glycosuria make this less likely.

(Choice C) Bladder infection (cystitis) can cause irritation of the bladder wall and findings similar to urge incontinence with urinary urgency, frequency, and incontinence. However, this patient's relatively normal urinalysis (no leukocyte esterase, hematuria, or bacteria seen) makes this less likely. Up to 5 wbc/hpf is normal.

(Choice D) Stress incontinence occurs in patients with sphincter dysfunction or weakness when intraabdominal pressure exceeds the urethral sphincter pressure (eg, sneezing, coughing), causing involuntary urine leakage. This patient's absence of urinary leakage with coughing or sneezing makes this less likely.

Educational objective:
Patients with multiple sclerosis most commonly develop urge incontinence due to loss of central nervous system inhibition of detrusor contraction in the bladder. As the disease progresses, the bladder can become atonic and dilated, leading to overflow incontinence.

References

- Multiple sclerosis produces significant changes in urinary bladder innervation which are partially reflected in the

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A 55-year-old woman is treated with ramipril for primary (essential) hypertension. Her blood pressure decreases to normal value over several weeks of treatment. The patient seems to be compliant with her medication and experiences no significant side effects. She has no other medical issues and takes no other medications. She does not use tobacco, alcohol, or illicit drugs. Physical examination shows no abnormalities. Which of the following is the most likely combination of changes in response to this patient's treatment (AT = angiotensin)?

	Renin	AT I	AT II	Aldosterone	Bradykinin
○ A.	↑	↑	↓	↓	↑
○ B.	↑	↑	↑	↓	↑
○ C.	↑	↑	↑	↓	No change
○ D.	↑	↑	↓	↓	↓
○ E.	↑	↓	↓	↓	↓
○ F.	↓	↓	↓	↓	No change

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A 55-year-old woman is treated with ramipril for primary (essential) hypertension. Her blood pressure decreases to normal value over several weeks of treatment. The patient seems to be compliant with her medication and experiences no significant side effects. She has no other medical issues and takes no other medications. She does not use tobacco, alcohol, or illicit drugs. Physical examination shows no abnormalities. Which of the following is the most likely combination of changes in response to this patient's treatment (AT = angiotensin)?

	Renin	AT I	AT II	Aldosterone	Bradykinin	
✓ A.	↑	↑	↓	↓	↑	(85%)
✗ B.	↑	↑	↑	↓	↑	(2%)
C.	↑	↑	↑	↓	No change	(1%)
D.	↑	↑	↓	↓	↓	(6%)
E.	↑	↓	↓	↓	↓	(1%)
F.	↓	↓	↓	↓	No change	(3%)

Incorrect
Correct answer
A

85%
Answered correctly

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Explanation

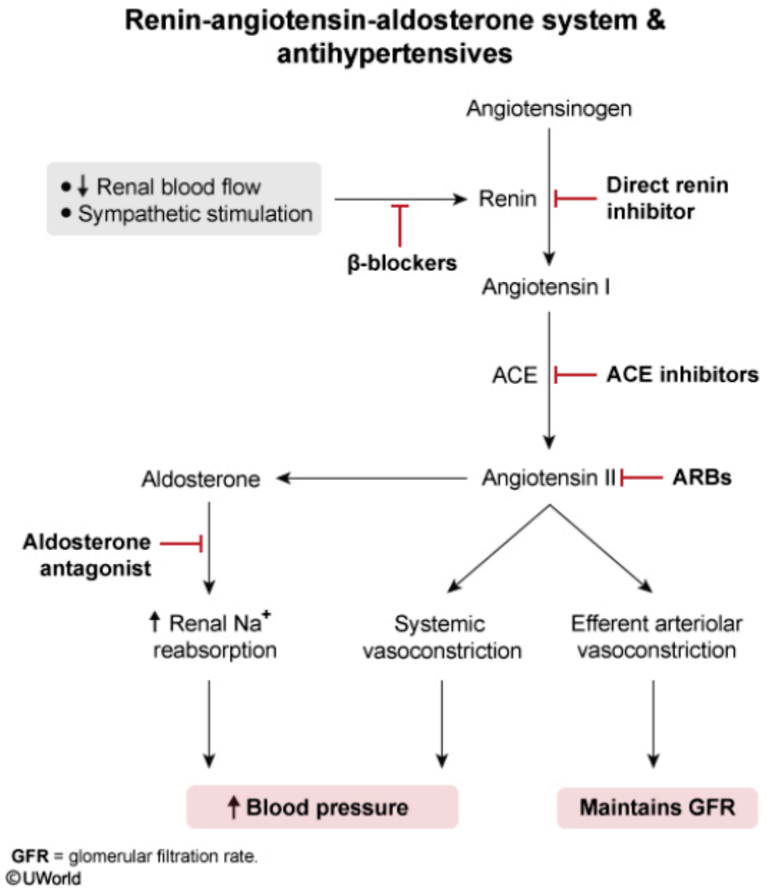
Renin-angiotensin-aldosterone system & antihypertensives

Angiotensinogen

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B. ↑ ↑ ↑ ↓ ↑ (2%)

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The renin-angiotensin-aldosterone system (RAAS) is one of the most important neurohormonal systems, regulating arterial blood pressure and sodium and fluid content in the body. In response to decreased sodium, fluid volume, or arterial blood pressure, renin is released from the kidneys, converting angiotensinogen to angiotensin I. Subsequently, angiotensin-converting enzyme (ACE) converts angiotensin I to angiotensin II. Angiotensin II then increases aldosterone secretion from the adrenal cortex, leading to increased sodium and fluid retention in the collecting tubules of the kidneys. Angiotensin II is also a potent vasoconstrictor that ultimately increases systemic vascular resistance and arterial pressure.

Angiotensin II itself is involved in 2 negative feedback mechanisms that help regulate the RAAS. In short-loop negative feedback, elevated angiotensin II stimulates the angiotensin receptors on juxtaglomerular cells to inhibit renin release. In long-loop negative feedback, increased blood pressure and sodium levels (due to angiotensin II) eventually decrease renin release via intrarenal baroreceptor and macula densa pathways, respectively.

ACE inhibitors such as ramipril block ACE and decrease the conversion of angiotensin I to angiotensin II, effectively blocking arteriolar vasoconstriction and aldosterone secretion. In addition to decreased blood pressure and sodium levels, **decreased angiotensin II** levels also interfere with negative feedback mechanisms, ultimately activating the RAAS to **promote renin release**. ACE is also responsible for the breakdown of bradykinin; therefore, ACE inhibitors lead to i**ncreased bradykinin** levels, which are thought to cause the characteristic ACE inhibitor–induced cough.

Educational objective:
Angiotensin-converting enzyme (ACE) inhibitors block the effect of ACE, decreasing angiotensin II and aldosterone levels. By decreasing angiotensin II levels, ACE inhibitors directly interrupt negative feedback loops, thereby increasing renin and angiotensin I levels. ACE is also responsible for the breakdown of bradykinin; ACE inhibitors therefore increase bradykinin levels.

Pharmacology | Renal, Urinary Systems & Electrolytes | Renin angiotensin aldosterone system

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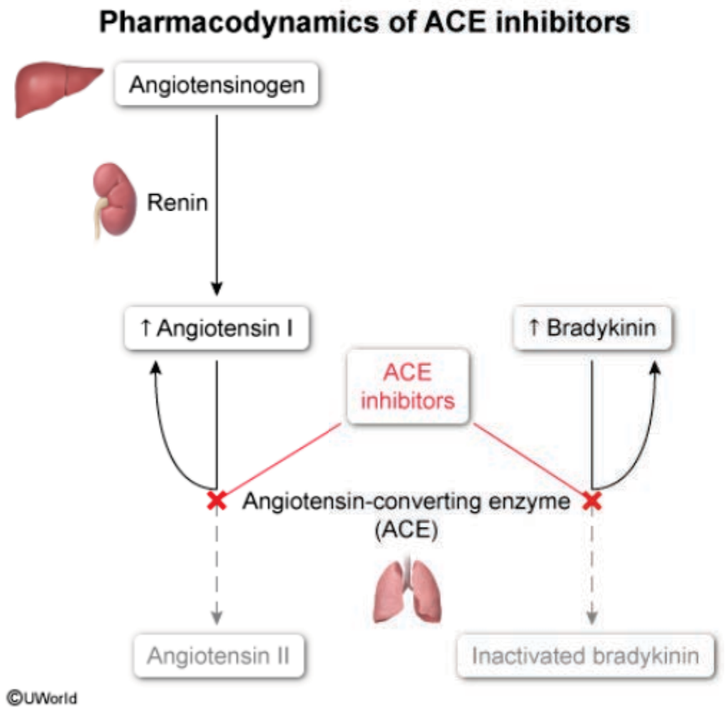
The renin-angiotensin-aldosterone system (RAAS) is one of the most important neurohormonal systems regulating
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Pharmacology | Renal, Urinary Systems & Electrolytes | Renin angiotensin aldosterone system

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A nephrology researcher conducts a clinical study to determine the risk factors for the development of renal calculi. He recruits a number of patients with a history of idiopathic calcium oxalate kidney stones, along with age- and sex-matched healthy subjects. Detailed medical, surgical, and nutritional histories are obtained, and several serum and urine laboratory tests are performed. Which of the following is most likely to be seen in affected patients compared with healthy individuals?

- A. Higher dietary calcium
- B. Higher dietary potassium
- C. Higher fluid intake
- D. Lower dietary oxalate
- E. Lower urinary citrate

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- A. Higher dietary calcium (22%)
- ✗ B. Higher dietary potassium (3%)
- C. Higher fluid intake (1%)
- D. Lower dietary oxalate (8%)
- ✓ E. Lower urinary citrate (63%)

Incorrect
Correct answer
E

63%
Answered correctly

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Explanation

Risk & prevention of kidney stones		
Stone type	**Risk factors**	**Prevention**
Calcium stones	• Hypercalciuria (eg, hyperparathyroidism) • Hyperoxaluria (eg, malabsorption, low-calcium diet)	• Reduce sodium, animal protein, oxalate intake • Increase potassium intake;

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Risk & prevention of kidney stones		
Stone type	**Risk factors**	**Prevention**
Calcium stones (oxalate, phosphate)	• Hypercalciuria (eg, hyperparathyroidism) • Hyperoxaluria (eg, malabsorption, low-calcium diet) • Hypocitraturia (eg, distal RTA) • Diet: ↑ sodium, ↑ protein, ↑ oxalate, ↓ calcium	• Reduce sodium, animal protein, oxalate intake • Increase potassium intake; moderate calcium intake • Thiazide diuretics
Uric acid	• Gout • Myeloproliferative disorders	• Urine alkalinization • Allopurinol
Magnesium ammonium phosphate (struvite)	• Recurrent upper urinary infection (eg, *Klebsiella*, *Proteus*)	• Stone removal • Suppressive antibiotics
All types	• Dehydration	• Increase fluid intake
RTA = renal tubular acidosis.		

Renal calculi occur due to an imbalance of the factors that facilitate or prevent stone formation. Overall, increased urinary concentrations of calcium (hypercalciuria), oxalate (hyperoxaluria), and uric acid (hyperuricosuria) promote salt crystallization, whereas increased urinary citrate and high fluid intake inhibit calculi formation.

Normally, **citrate** excreted by the kidneys **binds to ionized calcium** in the urine, **preventing** the formation of **insoluble calcium-oxalate complexes**. When urinary citrate is low (**hypocitraturia**), increased calcium availability leads to formation of calcium-oxalate complexes that can precipitate and form **calcium oxalate stones**. Hypocitraturia often occurs in the setting of chronic metabolic acidosis (eg, distal renal tubular acidosis,

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Renal calculi occur due to an imbalance of the factors that facilitate or prevent stone formation. Overall, increased urinary concentrations of calcium (hypercalciuria), oxalate (hyperoxaluria), and uric acid (hyperuricosuria) promote salt crystallization, whereas increased urinary citrate and high fluid intake inhibit calculi formation.

Normally, **citrate** excreted by the kidneys **binds to ionized calcium** in the urine, **preventing** the formation of **insoluble calcium-oxalate complexes**. When urinary citrate is low (**hypocitraturia**), increased calcium availability leads to formation of calcium-oxalate complexes that can precipitate and form **calcium oxalate stones**. Hypocitraturia often occurs in the setting of chronic metabolic acidosis (eg, distal renal tubular acidosis, chronic diarrhea) due to enhanced renal citrate reabsorption. Supplemental oral potassium citrate is often prescribed to prevent recurrent calcium stones.

(Choice A) Individuals with higher (but not excessive) calcium intake paradoxically have a lower risk of calcium oxalate stone formation. Dietary calcium binds oxalate in the gut to form insoluble calcium oxalate, which is eliminated in the feces. This reduces the amount of oxalate absorbed into the body and excreted in the urine, reducing stone formation.

(Choice B) In patients with inadequate dietary intake of potassium, increased tubular reabsorption of potassium leads to increased citrate reabsorption, which facilitates formation of calcium oxalate complexes in the renal tubules. Higher potassium intake promotes urinary excretion of citrate and lowers urinary calcium excretion, leading to a lower risk of calcium oxalate stones.

(Choice C) High fluid intake prevents supersaturation of urine with stone-forming ingredients. Low fluid intake increases the urinary concentration of these ions regardless of their absolute amounts, promoting stone formation.

(Choice D) Excessive oxalate intake (eg, chocolate, spinach, rhubarb) leads to increased intestinal absorption of free oxalate, which is then excreted in the urine where it promotes formation of calcium oxalate stones. Intestinal malabsorption syndromes (eg, Crohn disease) can also cause hyperoxaluria because calcium becomes bound by unabsorbed lipids in the gut.

Educational objective:

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Normally, **citrate** excreted by the kidneys **binds to ionized calcium** in the urine, **preventing** the formation of **insoluble calcium-oxalate complexes**. When urinary citrate is low (**hypocitraturia**), increased calcium availability leads to formation of calcium-oxalate complexes that can precipitate and form **calcium oxalate stones**. Hypocitraturia often occurs in the setting of chronic metabolic acidosis (eg, distal renal tubular acidosis, chronic diarrhea) due to enhanced renal citrate reabsorption. Supplemental oral potassium citrate is often prescribed to prevent recurrent calcium stones.

(Choice A) Individuals with higher (but not excessive) calcium intake paradoxically have a lower risk of calcium oxalate stone formation. Dietary calcium binds oxalate in the gut to form insoluble calcium oxalate, which is eliminated in the feces. This reduces the amount of oxalate absorbed into the body and excreted in the urine, reducing stone formation.

(Choice B) In patients with inadequate dietary intake of potassium, increased tubular reabsorption of potassium leads to increased citrate reabsorption, which facilitates formation of calcium oxalate complexes in the renal tubules. Higher potassium intake promotes urinary excretion of citrate and lowers urinary calcium excretion, leading to a lower risk of calcium oxalate stones.

(Choice C) High fluid intake prevents supersaturation of urine with stone-forming ingredients. Low fluid intake increases the urinary concentration of these ions regardless of their absolute amounts, promoting stone formation.

(Choice D) Excessive oxalate intake (eg, chocolate, spinach, rhubarb) leads to increased intestinal absorption of free oxalate, which is then excreted in the urine where it promotes formation of calcium oxalate stones. Intestinal malabsorption syndromes (eg, Crohn disease) can also cause hyperoxaluria because calcium becomes bound by unabsorbed lipids in the gut.

Educational objective:
Renal calculi occur due to an imbalance of the factors that facilitate or inhibit stone formation. Increased urinary concentrations of calcium, oxalate, and uric acid promote salt crystallization, whereas increased urinary citrate concentration and high fluid intake prevent calculi formation.

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Four children and 2 adults are currently being followed in a nephrology clinic for poststreptococcal glomerulonephritis. Three patients initially had gross hematuria and edema requiring diuretic administration. The remaining 3 patients had microscopic hematuria and hypertension. C3 levels were decreased in all patients, and antistreptolysin O titer was elevated in 4 of them. None of the patients have preexisting renal disease. Which of the following patient characteristics is most likely to indicate a poor long-term prognosis?

- A. Adult onset
- B. Decreased C3 level
- C. Delay in corticosteroid treatment
- D. Elevated antistreptolysin titer
- E. Gross hematuria

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Four children and 2 adults are currently being followed in a nephrology clinic for poststreptococcal glomerulonephritis. Three patients initially had gross hematuria and edema requiring diuretic administration. The remaining 3 patients had microscopic hematuria and hypertension. C3 levels were decreased in all patients, and antistreptolysin O titer was elevated in 4 of them. None of the patients have preexisting renal disease. Which of the following patient characteristics is most likely to indicate a poor long-term prognosis?

- ✓ A. Adult onset (66%)
- ✗ B. Decreased C3 level (8%)
- C. Delay in corticosteroid treatment (11%)
- D. Elevated antistreptolysin titer (5%)
- E. Gross hematuria (7%)

Incorrect
Correct answer
A

66%
Answered correctly

03 secs
Time Spent

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Explanation

Poststreptococcal glomerulonephritis (PSGN) is the most common cause of acute pediatric glomerulonephritis (GN) and presents with acute onset of malaise, periorbital **edema**, **hypertension**, and either microscopic or gross **hematuria**. Symptoms generally occur 1-3 weeks following group A streptococcal pharyngitis or skin infection (eg, impetigo). The lag in symptoms corresponds to formation and deposition of the streptococcal antigen and antibody complex within the glomerular basement membrane and the subsequent activation of complement.

PSGN most commonly affects children age 5-12, and >95% recover completely. **Increased age**, conversely, is the

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Poststreptococcal glomerulonephritis (PSGN) is the most common cause of acute pediatric glomerulonephritis (GN) and presents with acute onset of malaise, periorbital **edema**, **hypertension**, and either microscopic or gross **hematuria**. Symptoms generally occur 1-3 weeks following group A streptococcal pharyngitis or skin infection (eg, impetigo). The lag in symptoms corresponds to formation and deposition of the streptococcal antigen and antibody complex within the glomerular basement membrane and the subsequent activation of complement.

PSGN most commonly affects children age 5-12, and >95% recover completely. **Increased age**, conversely, is the most important **poor prognostic factor**; only 60% of adult cases resolve completely, and many of the remainder have residual hypertension, recurrent proteinuria, chronic renal insufficiency, or rapidly progressive GN resulting in end-stage renal disease.

(Choices B, D, and E) Elevated antistreptolysin O (ASO) titers and low C3 levels are present in the vast majority of patients with PSGN. ASO titers indicate recent streptococcal (usually pharyngeal) infection. C3 is decreased due to complement activation with deposition in the glomerulus. Initial urinalysis may show hematuria, proteinuria, and red blood cell casts, but none of these findings affect prognosis.

(Choice C) Corticosteroids are used in minimal change disease (the most common cause of nephrotic syndrome in children) but not in PSGN.

Educational objective:
Poststreptococcal glomerulonephritis presents with edema, hypertension, and hematuria after a streptococcal infection. Most children recover completely, but adult patients have a relatively poor prognosis and higher risk of chronic hypertension and renal insufficiency.

References

- Post-streptococcal glomerulonephritis.

Pathology	Renal, Urinary Systems & Electrolytes	Poststreptococcal Glomerulonephritis

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A 63-year-old man comes to the emergency department due to muscle weakness with severe cramping in the lower extremities. The cramps are severe enough to disrupt his sleep. The patient also exercises daily but has had to suspend his exercise regimen in the last 3 days due to the symptoms. Past medical history is notable for hypertension, for which he was started on chlorthalidone and amlodipine 4 weeks ago. Blood pressure in the emergency department is 140/86 mm Hg and pulse is 90/min. The heart has a regular rate and rhythm, and he has palpable pedal pulses with no peripheral edema. Which of the following is the most likely cause of this patient's muscular symptoms?

- A. Hyperuricemia
- B. Hypocalcemia
- C. Hypoglycemia
- D. Hypokalemia
- E. Hyponatremia
- F. Hypophosphatemia

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A 63-year-old man comes to the emergency department due to muscle weakness with severe cramping in the lower extremities. The cramps are severe enough to disrupt his sleep. The patient also exercises daily but has had to suspend his exercise regimen in the last 3 days due to the symptoms. Past medical history is notable for hypertension, for which he was started on chlorthalidone and amlodipine 4 weeks ago. Blood pressure in the emergency department is 140/86 mm Hg and pulse is 90/min. The heart has a regular rate and rhythm, and he has palpable pedal pulses with no peripheral edema. Which of the following is the most likely cause of this patient's muscular symptoms?

- A. Hyperuricemia (5%)
- ✗ B. Hypocalcemia (25%)
- C. Hypoglycemia (1%)
- ✓ D. Hypokalemia (58%)
- E. Hyponatremia (6%)
- F. Hypophosphatemia (2%)

Incorrect
Correct answer
D

58%
Answered correctly

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Time Spent

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Explanation

Thiazide diuretics lower blood pressure by decreasing **intravascular volume**, reducing cardiac output, and lowering systemic vascular resistance. Thiazides inhibit Na^+/Cl^- co-transporters in the distal convoluted tubules, thereby decreasing reabsorption of Na^+ and Cl^-. The decrease in intravascular volume is partially attenuated by

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Thiazide diuretics lower blood pressure by decreasing **intravascular volume**, reducing cardiac output, and lowering systemic vascular resistance. Thiazides inhibit Na^+/Cl^- co-transporters in the distal convoluted tubules, thereby decreasing reabsorption of Na^+ and Cl^-. The decrease in intravascular volume is partially attenuated by activation of the **renin-angiotensin-aldosterone** system. However, the rise in aldosterone secretion leads to increased urinary excretion of potassium and hydrogen ions, with resulting **hypokalemia** and metabolic alkalosis.

Chlorthalidone appears to be more potent in lowering blood pressure than other thiazides (eg, hydrochlorothiazide) but is also associated with more metabolic abnormalities. Significant hypokalemia can cause **muscle weakness**, cramps, and possible rhabdomyolysis.

(Choice A) Hypovolemia stimulates uric acid reabsorption in the proximal tubules. This can cause hyperuricemia and potentially precipitate a gout attack (acute monoarticular arthritis).

(Choice B) Thiazides increase calcium reabsorption in the distal convoluted tubules, reducing urinary excretion of calcium and modestly raising serum calcium levels. They do not cause hypocalcemia.

(Choice C) Thiazides decrease insulin secretion and peripheral uptake of glucose. This can cause hyperglycemia, not hypoglycemia.

(Choice E) Thiazides can cause hyponatremia due to increased urinary excretion of sodium. Acute hyponatremia causes nausea, malaise, headache, and central nervous symptoms (eg, altered mental status, seizures). Muscle cramps are less common and usually seen with chronic hyponatremia.

(Choice F) Hypophosphatemia can cause muscle weakness and paralysis but is not a side effect of thiazides. It is commonly seen with chronic alcohol use.

Educational objective:
Thiazide diuretics decrease intravascular fluid volume, which stimulates aldosterone secretion and leads to increased excretion of potassium and hydrogen ions in the urine. This results in hypokalemia and metabolic alkalosis.

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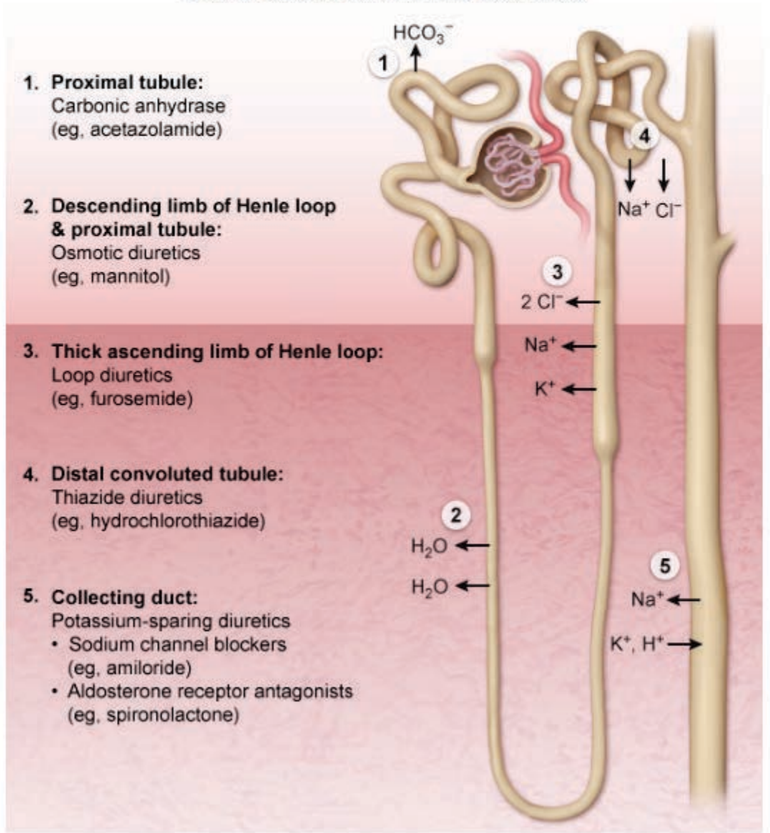
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Site of action for various diuretics



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Thiazide diuretics lower blood pressure by decreasing **intravascular volume**, reducing cardiac output, and

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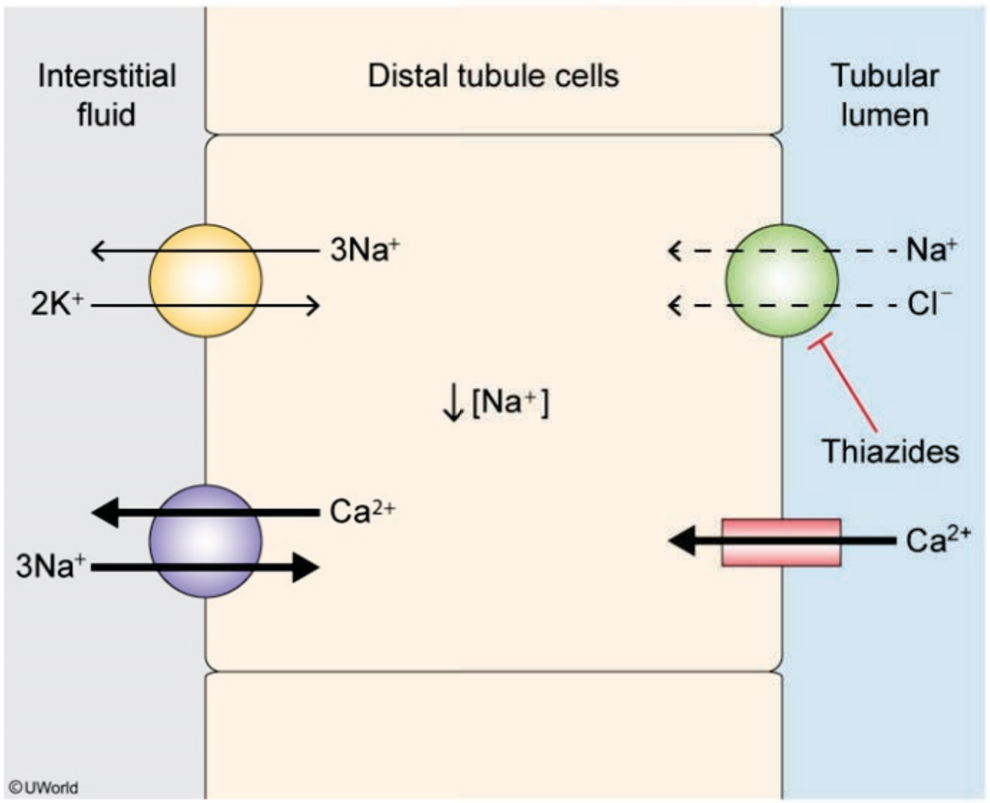
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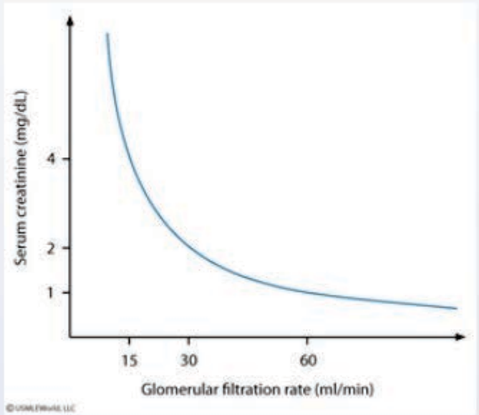


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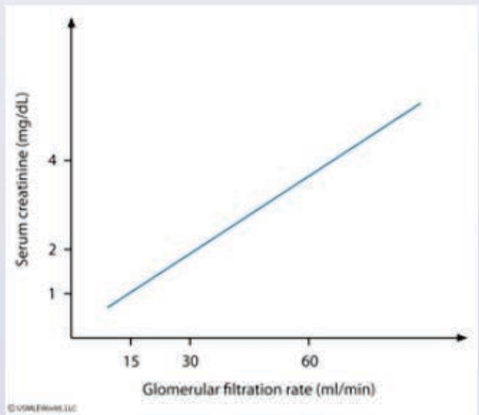
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A 65-year-old man with type 2 diabetes mellitus comes to the physician for a routine follow-up appointment. He was started on oral hypoglycemic medications 12 years ago but was recently switched to long-acting insulin due to inadequate blood sugar control. His last serum creatinine level was 2.1 mg/dL. The patient is concerned about his elevated creatinine level and how it relates to his kidney function. Which of the following graphs most accurately represents the relationship between serum creatinine and glomerular filtration rate?

A.



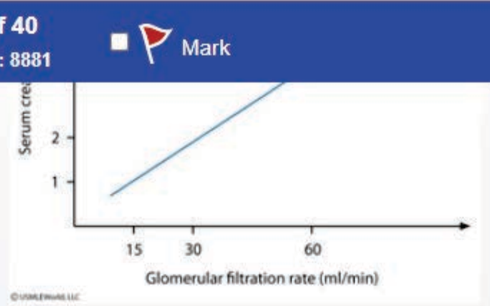
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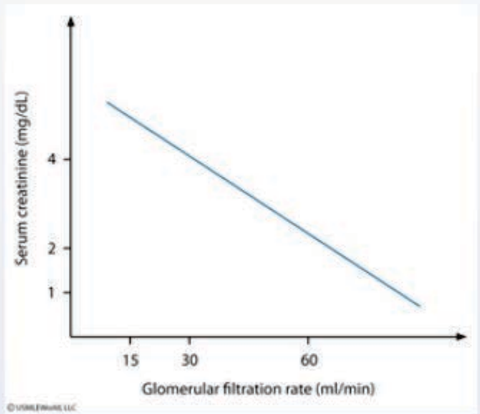
C.



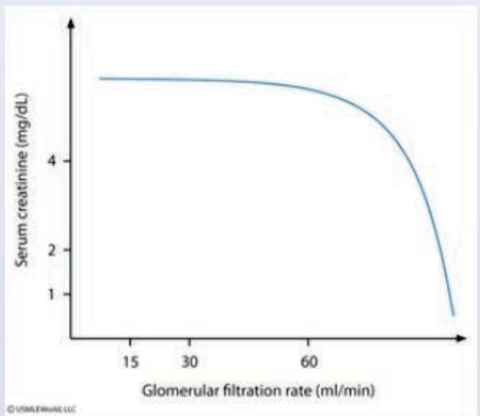
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C.



D.

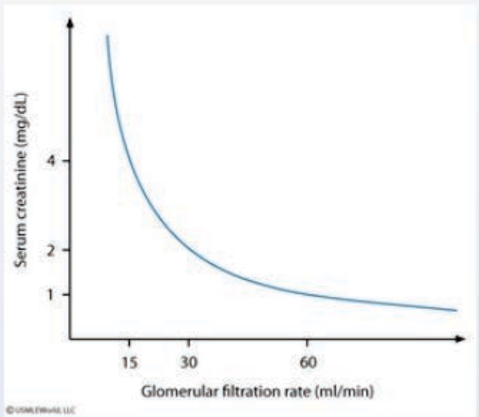


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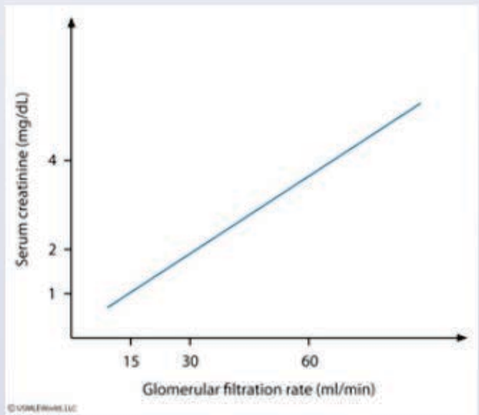
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✓ ○ A. (61%)



○ B. (9%)

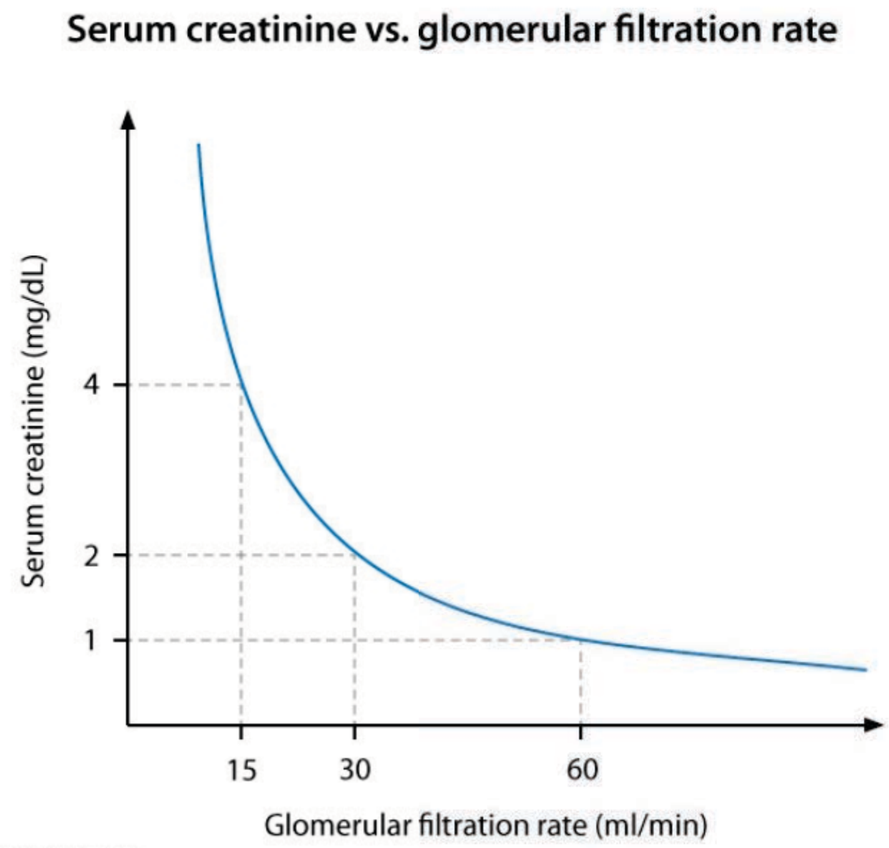


○ C. (22%)



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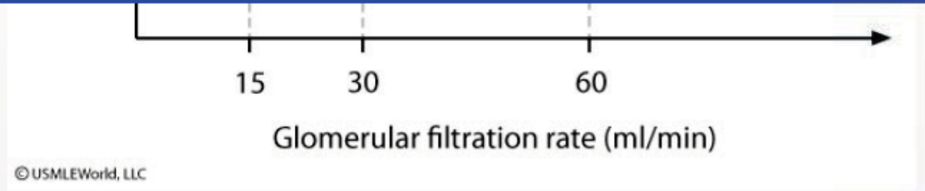
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Serum creatinine is the most common indicator of kidney function in clinical use. Steady-state creatinine levels are a result of the balance between creatinine synthesis in the muscle and excretion via glomerular filtration and proximal tubule secretion. For the most part, creatinine synthesis and tubular secretion remain relatively constant. As a result, serum creatinine levels depend primarily on the glomerular filtration rate (GFR).

The relationship between serum creatinine and GFR is nonlinear. A person's serum creatinine can be essentially normal even after a 50% loss of kidney function (ie, following kidney donation or unilateral nephrectomy). Serum creatinine levels begin to rise significantly as the GFR declines to <60 mL/min (assuming no change in muscle mass). As the GFR continues to decline, the slope of the creatinine-GFR curve steepens. Consequently, when the GFR is significantly decreased, small decrements in GFR produce relatively large changes in serum creatinine. However, when the GFR is normal, relatively large decreases in GFR result in only small increases in serum creatinine. Serum creatinine is therefore an insensitive indicator for decreasing GFR when creatinine levels are normal.

Educational objective:
When the glomerular filtration rate (GFR) is normal, relatively large decreases in GFR result in only small increases in serum creatinine. Conversely, when the GFR is significantly decreased, small decrements in GFR produce relatively large changes in serum creatinine. A good rule of thumb is that every time GFR halves, serum creatinine doubles.

Physiology	Renal, Urinary Systems & Electrolytes	Chronic kidney disease
Subject	System	Topic

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A 70-year-old man comes to the office due to increasing headaches, nausea, and vomiting. The patient has never had these symptoms before. Medical history is significant for a transient ischemic attack that led to a right carotid endarterectomy 5 years ago. He has no other medical conditions, and his only medications are aspirin and atorvastatin. The patient smoked a pack of cigarettes a day for 20 years but quit 20 years ago. Blood pressure is 220/120 mm Hg and pulse is 70/min. Neurologic examination shows no focal lesions. Bilateral abdominal bruits are present. Blood testing in this patient would most likely show which of the following?

	Renin	Aldosterone	Angiotensin II	Potassium
○ A.	↑	↑	↑	↑
○ B.	↑	↑	↑	↓
○ C.	↑	↑	↓	↓
○ D.	↑	↓	↓	↓
○ E.	↓	↓	↓	↓
○ F.	↓	↓	↓	↑
○ G.	↓	↓	↑	↑
○ H.	↓	↑	↑	↑

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	Renin	Aldosterone	Angiotensin II	Potassium	
✗ A.	↑	↑	↑	↑	(5%)
✓ B.	↑	↑	↑	↓	(80%)
C.	↑	↑	↓	↓	(0%)
D.	↑	↓	↓	↓	(0%)
E.	↓	↓	↓	↓	(1%)
F.	↓	↓	↓	↑	(9%)
G.	↓	↓	↑	↑	(0%)
H.	↓	↑	↑	↑	(0%)

Incorrect
Correct answer
B

80%
Answered correctly

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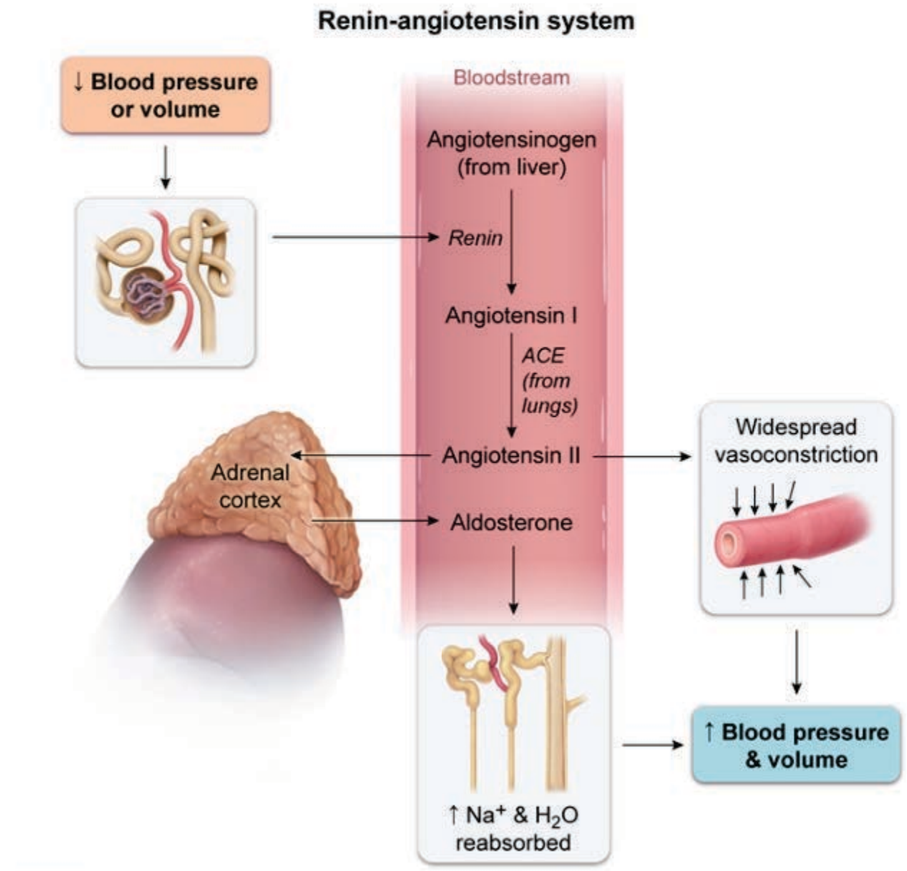
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Explanation

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Explanation

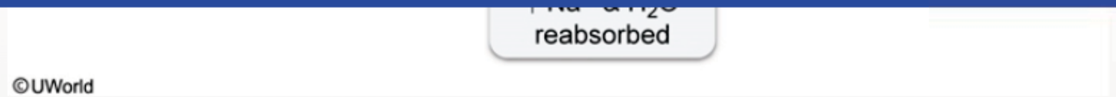
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This patient has a hypertensive emergency, with markedly elevated blood pressure and symptoms (headache, vomiting) suggesting elevated intracranial pressure. In conjunction with his bilateral **abdominal bruits** (abnormal sound caused by turbulent blood flow), this presentation suggests renovascular hypertension from **bilateral renal artery stenosis** (RAS). Although RAS can be caused by a variety of lesions (eg, fibromuscular dysplasia in young women), >90% of cases are caused by atherosclerotic narrowing of the proximal renal artery. Therefore, it is most common in older patients with other atherosclerotic disease (eg, carotid stenosis, as in this patient) or risk factors (eg, diabetes, hyperlipidemia, smoking).

Decreased renal artery perfusion activates the renin-angiotensin-aldosterone system. The juxtaglomerular cells increase secretion of **renin**, which converts angiotensinogen to angiotensin I. Angiotensin I is then converted to angiotensin II by angiotensin-converting enzyme. **Angiotensin II**, a potent vasoconstrictor, causes increased peripheral resistance and elevated systemic blood pressure. In addition, it stimulates the secretion of **aldosterone**, which increases renal Na^+ reabsorption and K^+ and H^+ excretion, resulting in relative **hypokalemia** and metabolic alkalosis.

Educational objective:
Renal artery stenosis (eg, severe hypertension, abdominal bruits) causes decreased renal artery perfusion, which activates the renin-angiotensin-aldosterone system. Increased secretion of renin leads to increased production of angiotensin I and angiotensin II, which causes increased peripheral resistance and elevated systemic blood pressure. Increased aldosterone secretion causes increased renal Na^+ reabsorption and K^+ and H^+ excretion, resulting in relative hypokalemia and metabolic alkalosis.

Pharmacology	Renal, Urinary Systems & Electrolytes	Renal artery stenosis
Subject	System	Topic

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Physiologists are studying the forces governing glomerular ultrafiltration using a single nephron in an intact kidney of an experimental animal. Hydrostatic pressure in the glomerular capillary and Bowman space is measured using micropipette transducers. Colloid osmotic pressure in the glomerular capillary is estimated using the difference in plasma protein concentration in the afferent and efferent arterioles. The glomerular surface is assumed to be functionally intact with negligible filtration of plasma proteins into the Bowman space. From the data obtained, net filtration pressure is calculated at 10 mm Hg. A substance is instilled into the renal artery, and measurements are repeated. The net filtration pressure after the intervention is 20 mm Hg. Which of the following substances was most likely used in this experiment?

- A. Albumin concentrate
- B. Alpha-adrenergic agonist
- C. Angiotensin II agonist
- D. Prostaglandin inhibitor
- E. Vasopressin 2 antagonist

Submit

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Physiologists are studying the forces governing glomerular ultrafiltration using a single nephron in an intact kidney of an experimental animal. Hydrostatic pressure in the glomerular capillary and Bowman space is measured using micropipette transducers. Colloid osmotic pressure in the glomerular capillary is estimated using the difference in plasma protein concentration in the afferent and efferent arterioles. The glomerular surface is assumed to be functionally intact with negligible filtration of plasma proteins into the Bowman space. From the data obtained, net filtration pressure is calculated at 10 mm Hg. A substance is instilled into the renal artery, and measurements are repeated. The net filtration pressure after the intervention is 20 mm Hg. Which of the following substances was most likely used in this experiment?

- A. Albumin concentrate (4%)
- ✗ B. Alpha-adrenergic agonist (4%)
- ✓ C. Angiotensin II agonist (79%)
- D. Prostaglandin inhibitor (6%)
- E. Vasopressin 2 antagonist (3%)

Incorrect
Correct answer
C

79%
Answered correctly

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Explanation

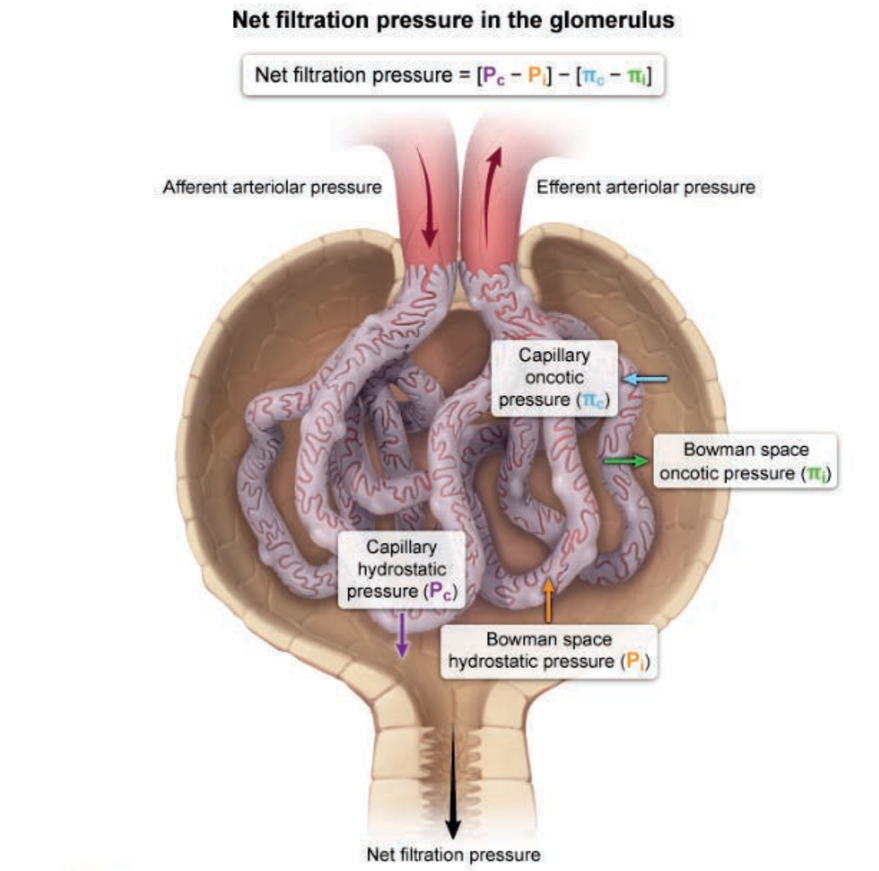
Net filtration pressure in the glomerulus

Net filtration pressure = $[P_c - P_i] - [\pi_c - \pi_i]$

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Net filtration pressure

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The net filtration pressure is a result of pressure gradients formed by Starling forces and is calculated by subtracting the oncotic pressure gradient from the hydrostatic pressure gradient (ie, net filtration pressure = $[P_c - P_i] - [\pi_c - \pi_i]$):

- **The hydrostatic pressure gradient** ($P_c - P_i$) is the difference between the hydrostatic pressure in the intraglomerular capillaries and Bowman's space. Hydrostatic pressure in the capillaries is higher than in Bowman's space, and provides the **driving force for fluid efflux** from the capillaries.
- **The oncotic pressure gradient** ($\pi_c - \pi_i$) is the difference between the oncotic pressure in the intraglomerular capillaries and Bowman's space. Oncotic pressure is driven chiefly by large plasma proteins (eg, albumin), which do not freely filter across the glomerular capillary basement membrane due to both a size and a charge barrier. The high oncotic pressure in the capillaries counteracts the capillary hydrostatic pressure and **decreases net fluid efflux** from the capillaries.

This patient's net **filtration pressure has increased** from 10 to 20 mm Hg after infusion of a substance. Increased net filtration pressure occurs due to either an increase in the hydrostatic pressure gradient or a decrease in the oncotic pressure gradient. Of the available options, only an **angiotensin II agonist** would increase the net filtration pressure. Angiotensin II preferentially **constricts the efferent arteriole**, resulting in an **increased hydrostatic pressure gradient** and increased net filtration pressure.

(Choice A) Albumin is not filtered across the glomerular capillary and would increase the oncotic pressure gradient, resulting in a lower net filtration pressure.

(Choice B) Alpha-1 receptors are located mainly in the afferent arteriole; alpha agonists (eg, epinephrine, norepinephrine) result in constriction of the afferent arteriole, which reduces hydrostatic pressure and leads to lower net filtration pressures.

(Choice D) Prostaglandins (eg, prostaglandin E2) are responsible for dilation of the afferent arteriole. Inhibition of

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decreases net fluid efflux from the capillaries.

This patient's net **filtration pressure has increased** from 10 to 20 mm Hg after infusion of a substance. Increased net filtration pressure occurs due to either an increase in the hydrostatic pressure gradient or a decrease in the oncotic pressure gradient. Of the available options, only an **angiotensin II agonist** would increase the net filtration pressure. Angiotensin II preferentially **constricts the efferent arteriole**, resulting in an **increased hydrostatic pressure gradient** and increased net filtration pressure.

(Choice A) Albumin is not filtered across the glomerular capillary and would increase the oncotic pressure gradient, resulting in a lower net filtration pressure.

(Choice B) Alpha-1 receptors are located mainly in the afferent arteriole; alpha agonists (eg, epinephrine, norepinephrine) result in constriction of the afferent arteriole, which reduces hydrostatic pressure and leads to lower net filtration pressures.

(Choice D) Prostaglandins (eg, prostaglandin E2) are responsible for dilation of the afferent arteriole. Inhibition of prostaglandin synthesis, as seen with nonsteroidal anti-inflammatory drugs, results in constriction of the afferent arteriole, leading to reduced hydrostatic pressure and a lower net filtration pressure.

(Choice E) Vasopressin 2 antagonists (eg, tolvaptan) reduce vasopressin-induced free water resorption. These drugs do not have a direct effect on the Starling forces; however, reduced free water resorption can result in decreased blood volume, which decreases capillary hydrostatic pressure, which would lower the net filtration pressure.

Educational objective:
The net filtration pressure is a result of pressure gradients formed by Starling forces and is calculated by subtracting the oncotic pressure gradient from the hydrostatic pressure gradient. Angiotensin II preferentially constricts the efferent arteriole, resulting in an increased hydrostatic pressure gradient and an increased net filtration pressure.

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A 21-year-old man is brought to the emergency department due to diffuse muscle aches and weakness. He has also noticed darkening of his urine. The patient recently joined the military and was participating in rigorous training exercises in hot weather earlier in the day. He has no significant medical conditions and takes no medications. Medical evaluation and laboratory testing performed prior to military enlistment showed no abnormalities. Temperature is 36.7 C (98 F), blood pressure is 100/60 mm Hg, pulse is 105/min, and respirations are 16/min. Physical examination shows dry mucous membranes and muscle tenderness over the bilateral thighs and calves. Laboratory results are as follows:

Sodium	136 mEq/L
Potassium	5.6 mEq/L
Chloride	100 mEq/L
Bicarbonate	18 mEq/L
Blood urea nitrogen	30 mg/dL
Creatinine	2.0 mg/dL
Calcium	6.8 mg/dL
Phosphorus	7.8 mg/dL
Creatine kinase	22,000 U/L (normal: 30-170)

Which of the following urine microscopy findings is most likely to be seen in this patient?

A. Dysmorphic red blood cells
B. Eosinophils
C. Granular casts

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and calves. Laboratory results are as follows:

Sodium	136 mEq/L
Potassium	5.6 mEq/L
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Which of the following urine microscopy findings is most likely to be seen in this patient?

- A. Dysmorphic red blood cells
- B. Eosinophils
- C. Granular casts
- D. Isomorphic red blood cells
- E. Polymorphonuclear leukocytes
- F. Red blood cell casts

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Which of the following urine microscopy findings is most likely to be seen in this patient?

- A. Dysmorphic red blood cells (15%)
- ✗ B. Eosinophils (1%)
- ✓ C. Granular casts (54%)
- D. Isomorphic red blood cells (11%)
- E. Polymorphonuclear leukocytes (1%)
- F. Red blood cell casts (16%)

Incorrect
Correct answer
C

54%
Answered correctly

12 mins, 32 secs
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Explanation

Urinary casts	Composition	Associated conditions
Hyaline	• Tamm-Horsfall protein	• Nonspecific, concentrated urine
Fatty	• Lipid droplets	• Nephrotic syndrome
Waxy	• Degenerated hyaline cast	• Chronic kidney disease
Granular (muddy brown)	• Sloughed tubular epithelial cells with pigmented granules	• Acute tubular necrosis
WBC	• White blood cells	• Pyelonephritis, interstitial nephritis
RBC	• Red blood cells	• Glomerulonephritis

This patient's presentation is consistent with **rhabdomyolysis**, which is characterized by skeletal muscle necrosis and the release of intracellular breakdown products into the circulation. The condition is most commonly caused by trauma, sepsis, drugs/toxins (eg, statins, alcohol, cocaine), and **overexertion** (particularly in hot climates). Patients classically have **myalgia and weakness** (predominantly in the proximal muscles, lower back, and calves) and dark urine (due to **myoglobinuria**). Laboratory studies often show markedly **elevated creatine kinase** levels and acute kidney injury with electrolyte disturbances (eg, hyperkalemia, hyperphosphatemia, hypocalcemia, metabolic acidosis).

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Acute kidney injury in rhabdomyolysis occurs due to myoglobin degradation and heme pigment release. Heme pigment causes acute tubular necrosis (ATN) through direct cytotoxicity and renal vasoconstriction (ie, ischemia). In ATN, injured tubular epithelial cells slough off into the tubular lumen, forming granular, muddy brown casts. Heme pigment in myoglobin cross-reacts with the urine dipstick reagent that detects hemoglobin, leading to a false-positive result for blood in urine; however, microscopy shows no red blood cells (RBCs).

(Choices A, D, and F) Dysmorphic RBCs and RBC casts are typically seen in patients with glomerulonephritis. Dysmorphic RBCs have abnormal shapes due to deformation as they pass through the glomerular basement membrane and osmotic stress in the renal tubules. Normal-appearing (isomorphic) RBCs are seen in nonglomerular sources of hematuria, such as nephrolithiasis or urinary tract malignancies.

(Choice B) Urinary eosinophils are suggestive of acute interstitial nephritis (AIN), although they may be associated with other conditions (eg, kidney transplant rejection, pyelonephritis). AIN results from immune-mediated tubulointerstitial injury often caused by medications (eg, nonsteroidal anti-inflammatory drugs, penicillins). Patients classically have some combination of rash, fever, and eosinophilia.

(Choice E) Polymorphonuclear leukocytes in the urine indicate inflammation, which most commonly occurs due to infection. Interstitial nephritis, renal tuberculosis, and gonorrhea/chlamydia urethritis should be considered in patients with negative urine cultures (sterile pyuria).

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(Choice E) Polymorphonuclear leukocytes in the urine indicate inflammation, which most commonly occurs due to infection. Interstitial nephritis, renal tuberculosis, and gonorrhea/chlamydia urethritis should be considered in patients with negative urine cultures (sterile pyuria).

Educational objective:
Rhabdomyolysis usually presents with myalgia, proximal muscle weakness, and dark urine (myoglobinuria) in the setting of trauma, sepsis, or overexertion. Kidney injury occurs due to heme pigment-mediated tubular injury, leading to acute tubular necrosis. Urine microscopy typically reveals granular, muddy brown casts.

Pathology	Renal, Urinary Systems & Electrolytes	Rhabdomyolysis
Subject	System	Topic

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by trauma, sepsis, drugs/toxins (eg, statins, alcohol, cocaine), and **overexertion** (particularly in hot climates).

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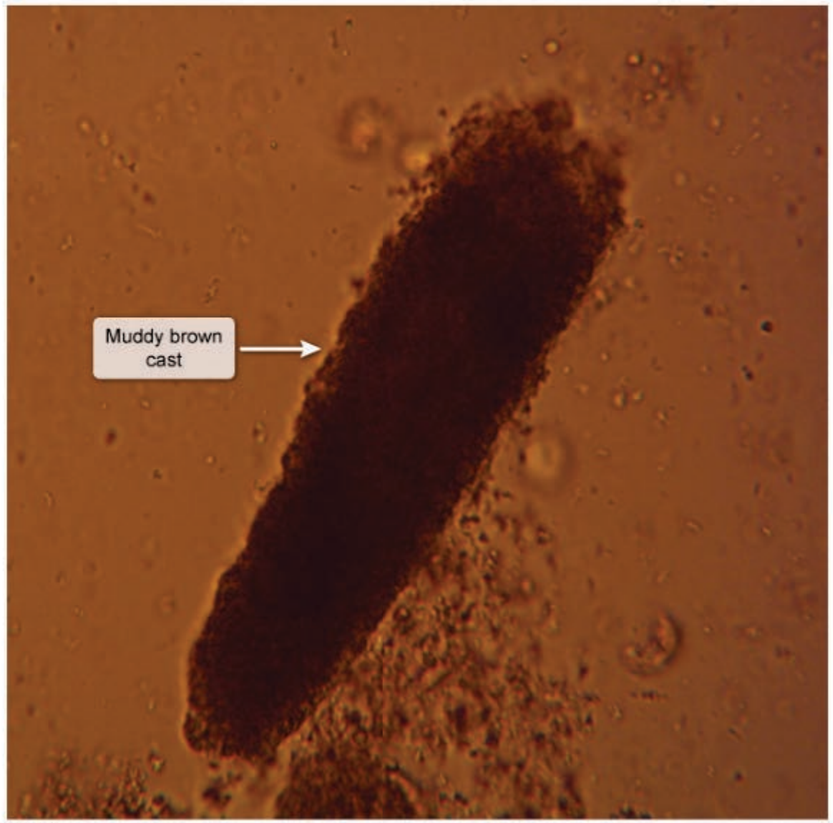
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Acute tubular necrosis



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A 68-year-old man comes to the office due to episodes of gross hematuria over the last 3 months. Blood is present throughout micturition. The patient has no abdominal pain, dysuria, urinary frequency, or nocturia. Medical history includes type 2 diabetes mellitus, for which he takes metformin. The patient is retired, lives at home with his wife, and spends most of his free time working in his backyard greenhouse. Prior to retirement, he worked at a rubber manufacturing plant for 35 years. Vital signs are within normal limits. On examination, the abdomen is soft and nontender with no palpable masses. Serum creatinine is 1.1 mg/dL. Which of the following is most likely to be discovered on further workup of this patient's symptoms?

- A. Bladder cancer
- B. Glomerulonephritis
- C. Interstitial cystitis
- D. Polycystic kidney disease
- E. Prostate cancer
- F. Staghorn calculus

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- ✓ A. Bladder cancer (89%)
- B. Glomerulonephritis (4%)
- ✗ C. Interstitial cystitis (2%)
- D. Polycystic kidney disease (0%)
- E. Prostate cancer (2%)
- F. Staghorn calculus (1%)

Incorrect
Correct answer
A

89%
Answered correctly

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Explanation

Specific cancer risk factors			
[illegible]	• Tobacco smoke	[illegible]	• Tobacco smoke [illegible]

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Specific cancer risk factors			
Pancreas	• Tobacco smoke • Obesity	**Renal**	• Tobacco smoke • Obesity • Hypertension
Gastric	• Dietary nitrates • Alcohol & tobacco use • *Helicobacter pylori*	**Bladder**	• Tobacco smoke • Occupational exposures (rubber, plastics, aromatic amine–containing dyes, textiles, leather)
Liver	• Hepatitis B & C • Liver cirrhosis (any cause) • Hemochromatosis • Aflatoxin	**Breast**	• Early menarche • Late menopause • Nulliparity • *BRCA* mutations
Colorectal	• Hereditary CRC syndromes • Inflammatory bowel disease • Obesity • Charred or fried foods	**Prostate**	• Increasing age • African American
CRC = colorectal cancer.			

This patient has intermittent, **painless gross hematuria**. In an older patient, this presentation raises suspicion for urinary tract cancer, especially **urothelial (transitional cell) bladder cancer** (UBC). The diagnosis of UBC can be confirmed by identifying erythematous sessile, nodular, or papillary lesions on cystoscopy. The malignant epithelial cells are pleomorphic and have hyperchromatic nuclei, an increased nucleus/cytoplasm ratio, and disrupted orientation and polarity (in relation to the basement membrane). Frequent mitotic figures may be present.

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UBC is most common in patients age >60, with men affected more often than women. Major risk factors include **cigarette smoking** and **occupational exposure** to rubber, plastics, aromatic amine–containing dyes, textiles, or leather. Cyclophosphamide therapy (eg, for lymphoma, autoimmune disorders) also increases the risk. In Africa and the Middle East, infection with *Schistosoma haematobium* is associated with multiple cell types of bladder cancer, including UBC and squamous cell carcinoma.

(Choice B) Glomerulonephritis can cause grossly red or tea-colored urine but more commonly causes microscopic hematuria with red cell casts and dysmorphic red blood cells.

(Choice C) Interstitial cystitis is characterized by bladder pain, urinary frequency, and dysuria. Gross hematuria is not typical.

(Choice D) Autosomal dominant polycystic kidney disease can cause hypertension, hematuria, and renal insufficiency. However, hypertension is usually present by age 40, and this patient has no other suggestive features (eg, renal insufficiency, palpable kidneys).

(Choice E) Prostate cancer is typically asymptomatic or discovered on evaluation for lower urinary tract voiding symptoms (eg, decreased force of stream, nocturia). Painless hematuria without voiding symptoms is more suggestive of bladder cancer.

(Choice F) Staghorn calculi are large magnesium ammonium phosphate (struvite) stones that fill the renal calyces. Although they may cause hematuria, they are typically seen in patients with recurrent urinary tract infections by urease-producing bacteria (eg, *Proteus*, *Klebsiella*).

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Educational objective:
Urothelial (transitional cell) bladder cancer typically affects the elderly and presents with gross hematuria. A history of smoking or occupational exposure to rubber, plastics, aromatic amine–containing dyes, textiles, or leather increases the risk.

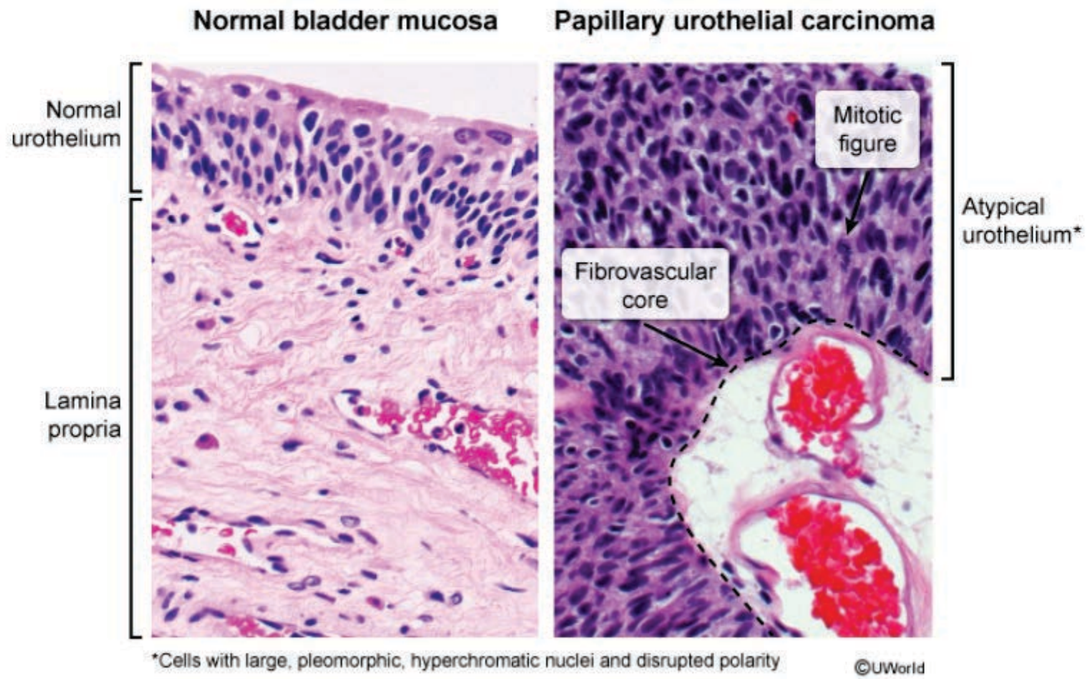
References

- Epidemiology and risk factors of urothelial bladder cancer.

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- Hereditary CRC syndromes

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(Choice E) Prostate cancer is typically asymptomatic or discovered on evaluation for lower urinary tract voiding

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A 32-year-old woman comes to the emergency department with sudden-onset left flank pain and nausea. The pain radiates to the left groin and she is unable to find a comfortable position on the examination table. The pain is intermittent and waxes and wanes in severity. Temperature is 36.7 C (98 F), blood pressure is 140/90 mm Hg, and pulse is 92/min. She has mild tenderness to percussion over the left flank. Bowel sounds are hypoactive. Which of the following recommendations would most likely prevent a recurrence of this patient's condition?

- A. Avoid alcohol use
- B. Complete a course of antibiotics
- C. Drink plenty of water daily
- D. Follow a high-fiber diet
- E. Follow a high-sodium diet
- F. Follow a low-calcium diet
- G. Follow safe sexual practices

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- A. Avoid alcohol use (1%)
- ✗ B. Complete a course of antibiotics (2%)
- ✓ C. Drink plenty of water daily (82%)
- D. Follow a high-fiber diet (6%)
- E. Follow a high-sodium diet (0%)
- F. Follow a low-calcium diet (5%)
- G. Follow safe sexual practices (2%)

Incorrect
Correct answer
C

82%
Answered correctly

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Explanation

Risk & prevention of kidney stones		
Stone type	**Risk factors**	**Prevention**
	• Hypercalciuria (eg, hyperparathyroidism)	

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Risk & prevention of kidney stones		
Stone type	**Risk factors**	**Prevention**
Calcium stones (oxalate, phosphate)	• Hypercalciuria (eg, hyperparathyroidism) • Hyperoxaluria (eg, malabsorption, low-calcium diet) • Hypocitraturia (eg, distal RTA) • Diet: ↑ sodium, ↑ protein, ↑ oxalate, ↓ calcium	• Reduce sodium, animal protein, oxalate intake • Increase potassium intake; moderate calcium intake • Thiazide diuretics
Uric acid	• Gout • Myeloproliferative disorders	• Urine alkalinization • Allopurinol
Magnesium ammonium phosphate (struvite)	• Recurrent upper urinary infection (eg, *Klebsiella*, *Proteus*)	• Stone removal • Suppressive antibiotics
All types	• Dehydration	• Increase fluid intake
RTA = renal tubular acidosis.		

This patient has acute flank pain and tenderness consistent with **nephrolithiasis**. The pain associated with nephrolithiasis (renal colic) is often severe and, although it may wax and wane, is generally not positional. The pain commonly radiates to the groin, especially as the stone passes down the ureter to the ureterovesical junction. Nausea and vomiting are common, and bowel sounds are often diminished due to an associated ileus. Hematuria is usually present but may not be grossly visible.

Most kidney stones are calcium-based (calcium oxalate, calcium phosphate). But regardless of chemical composition, low fluid intake can lead to **supersaturation** of urine with crystalline material and promote stone formation. **Increasing fluid intake** can reduce the risk of all types of stones.

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Most kidney stones are calcium-based (calcium oxalate, calcium phosphate). But regardless of chemical composition, low fluid intake can lead to **supersaturation** of urine with crystalline material and promote stone formation. **Increasing fluid intake** can reduce the risk of all types of stones.

(Choice A) Excessive alcohol intake can trigger acute pancreatitis. The pain associated with pancreatitis is typically located in the epigastric area rather than the flank and radiates to the back rather than the groin.

(Choice B) Recurrent infections of the upper urinary tract with urease-producing organisms (eg, *Klebsiella*, *Proteus*) can lead to formation of magnesium ammonium phosphate (struvite) stones. These stones are often large and may fill the renal pelvis. Although patients may have mild flank pain due to recurrent infection, acute renal colic is uncommon as these large stones do not travel down the ureter.

(Choice D) A high-fiber diet is associated with a decreased risk of diverticulitis. This condition typically presents over a few days (not suddenly, as in this patient) with lower abdominal pain and tenderness in the left lower quadrant.

(Choice E) Calcium passively follows the reabsorption of sodium and water in the renal tubules. Increased dietary sodium intake leads to reduced sodium reabsorption in the proximal tubule and lowers calcium reabsorption (leading to hypercalciuria).

(Choice F) Dietary calcium binds oxalate in the gut to form unabsorbable calcium oxalate. Low-calcium diets lead to increased absorption of free oxalate, which is then excreted in the urine; the resulting hyperoxaluria promotes the formation of calcium oxalate stones. Low-calcium diets are therefore paradoxically associated with increased risk of stone formation.

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(Choice A) Excessive alcohol intake can trigger acute pancreatitis. The pain associated with pancreatitis is typically located in the epigastric area rather than the flank and radiates to the back rather than the groin.

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(Choice G) Untreated infection with chlamydia or gonorrhea can lead to pelvic inflammatory disease, presenting with lower abdominal pain and fever. Examination findings include mucopurulent cervical discharge and cervical motion tenderness.

Educational objective:
Urine supersaturation is the main mechanism underlying all types of renal stones. Low fluid intake increases the concentration of stone-forming agents, thereby promoting stone formation. All patients with nephrolithiasis should be advised to maintain adequate fluid intake.

References

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The following vignette applies to the next 2 items. The items in the set must be answered in sequential order. Once you click Proceed to Next Item, you will not be able to add or change an answer.

A 72-year-old man is brought to the emergency department due to a 3-day history of fever, cough, and confusion. Temperature is 38.9 C (102 F), blood pressure is 70/50 mm Hg, and pulse is 112/min. On physical examination, the patient is lethargic but arousable. Coarse rhonchi are present over the right lung base. Chest x-ray reveals right lower lobe pneumonia. The patient is admitted in the intensive care unit, and intravenous fluids and broad-spectrum antibiotics are begun. In the hospital, the patient is noted to have low daily urine output measured from a urinary catheter. On day 3 of hospitalization, his serum creatinine is 3.6 mg/dL; it was 2.2 mg/dL at admission. The patient has no prior history of kidney disease. A renal biopsy image representative of this patient's disease process is shown in the exhibit.

Item 1 of 2

Which of the following is the most likely underlying cause of this patient's acute kidney injury?

- A. Glomerular inflammation
- B. Neutrophilic tubulitis
- C. Outer medullary ischemia
- D. Urinary tract obstruction
- E. Vascular fibrinoid necrosis

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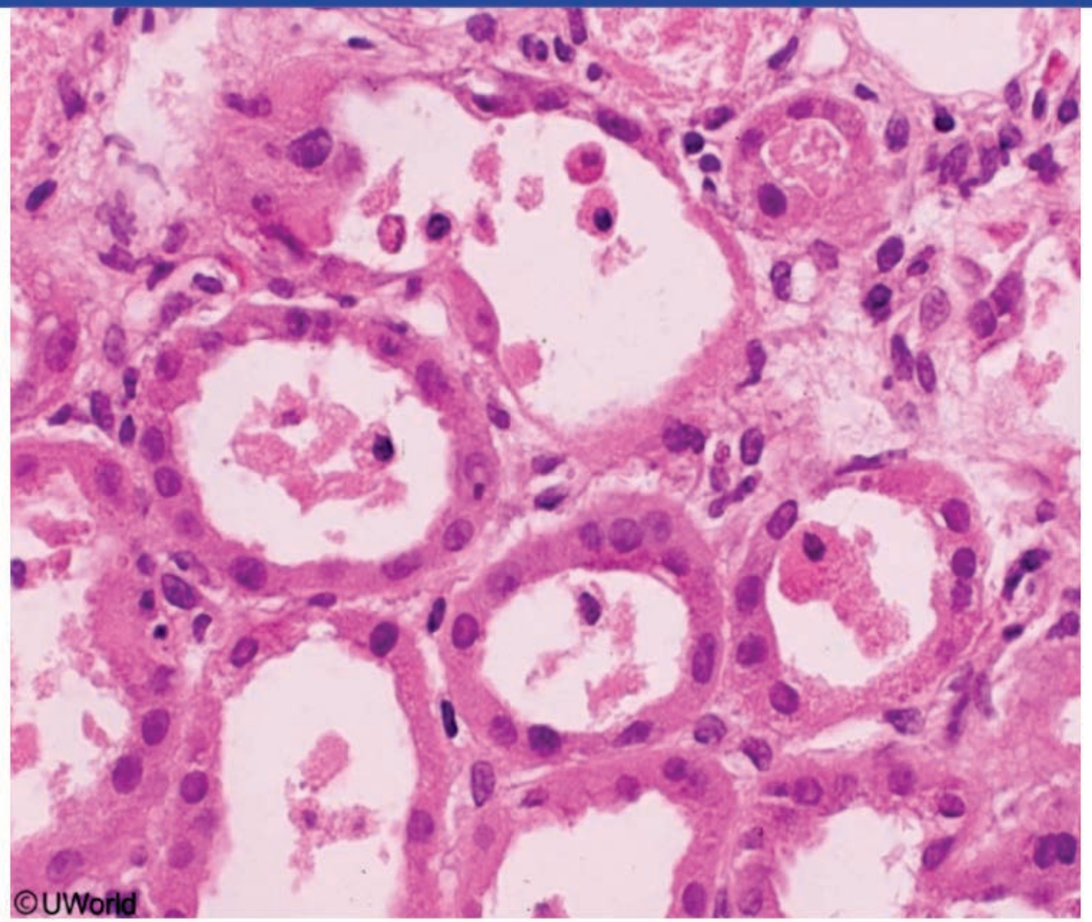
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Item 2 of 2

The patient's clinical condition gradually improves. On day 7 of hospitalization, his serum creatinine level is 1.1 mg/dL. Which of the following conditions would exhibit pathological kidney findings most similar to those observed in this patient?

- A. Diabetes mellitus
- B. Minimal change disease
- C. Severe rhabdomyolysis
- D. Systemic amyloidosis
- E. Systemic lupus erythematosus

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Item 1 of 2

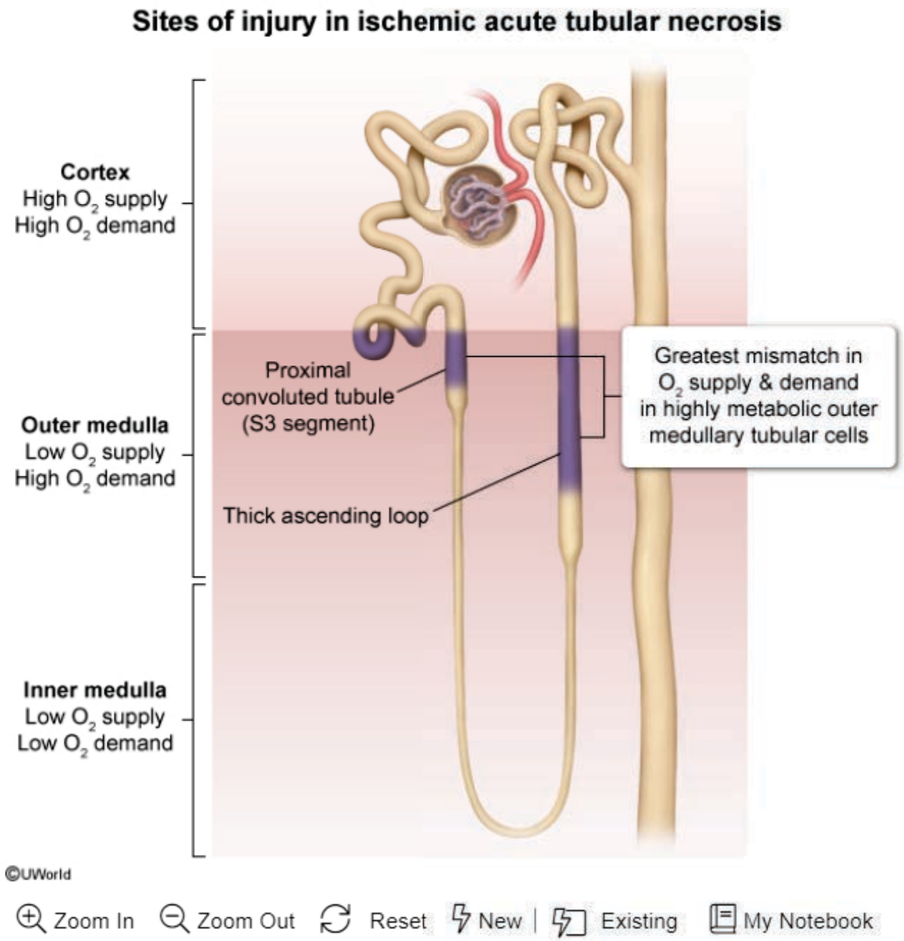
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- ✓ C. Outer medullary ischemia
- D. Urinary tract obstruction
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Ischemic ATN primarily affects the corticomedullary junction (which mostly contains the S3 segment of the proximal

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This patient initially had hypotension from sepsis caused by pneumonia. Despite receiving appropriate treatment, he has subsequently developed acute kidney injury with renal biopsy findings indicating **acute tubular necrosis** (ATN). ATN is most often caused by severe or prolonged **renal hypoperfusion**.

Ischemic ATN primarily affects the corticomedullary junction (which mostly contains the S3 segment of the proximal convoluted tubule [PCT]) and the **outer medulla** (which mostly contains the thick ascending loop [TAL]). These regions are most susceptible to ischemic injury due to a mismatch of oxygen demand and supply:

- **High oxygen demand:** Both PCT and TAL cells are highly dependent on active transport and therefore require a large amount of ATP. PCT cells have a particularly high oxygen demand because they rely on fatty acid oxidation (which generates significantly more ATP than anaerobic glycolysis used in other nephron regions).
- **Low oxygen supply:** Oxygen tension is lowest in the medulla due to blood flow in this region being entirely derived from postglomerular vessels. TAL cells are particularly affected by hypoxia because of their deeper location within the medulla.

In contrast, tubular cells in the innermost portion of the medulla (eg, collecting tubules) are largely spared in ischemic ATN. This is because despite having the lowest oxygen supply, these cells are less metabolically active (ie, low oxygen demand) and rely primarily on anaerobic glycolysis (ie, less affected by hypoxia).

(Choice A) Glomerular inflammation (ie, glomerulonephritis) is typically seen with certain infections (eg, hepatitis C, poststreptococcal) or autoimmune disease (eg, systemic lupus erythematosus), but it is not an expected complication of sepsis. Renal biopsy shows glomerular abnormalities (eg, hypercellularity).

(Choice B) Neutrophilic tubulitis is seen in patients with acute pyelonephritis, which does not typically cause AKI and is unlikely to develop in this patient receiving broad-spectrum antibiotics for pneumonia.

(Choice D) Prostate enlargement is a common cause of urinary tract obstruction in older men, but this is unlikely in this patient with low urine output from his urinary catheter (a large postcatheterization diuresis would be

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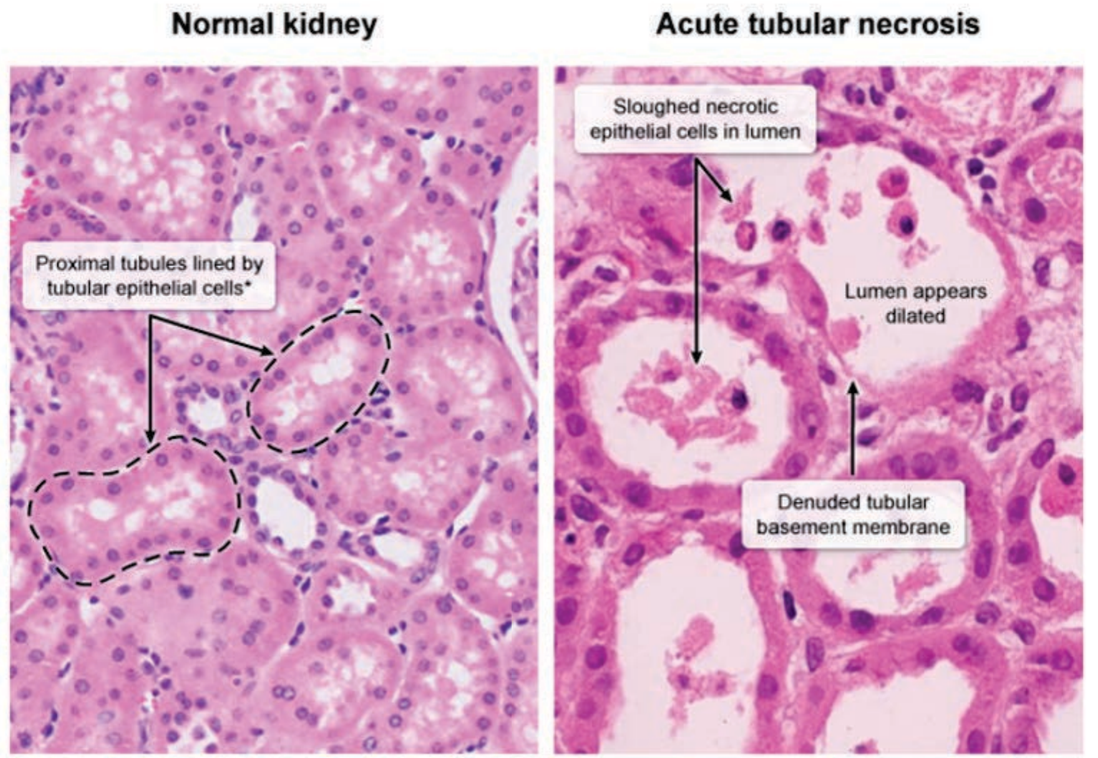
(Choice E) Vascular fibrinoid necrosis is a nonspecific biopsy finding signifying small blood vessel damage (eg, renal vasculitis, malignant nephrosclerosis). This patient's clinical presentation is more consistent with ATN, and no significant vascular findings are seen on biopsy.

Educational objective:
Ischemic acute tubular necrosis primarily involves the corticomedullary junction (ie, proximal convoluted tubule) and the outer medulla (ie, thick ascending loop) due to a mismatch in oxygen supply and demand.

Pathology Renal, Urinary Systems & Electrolytes Acute kidney injury

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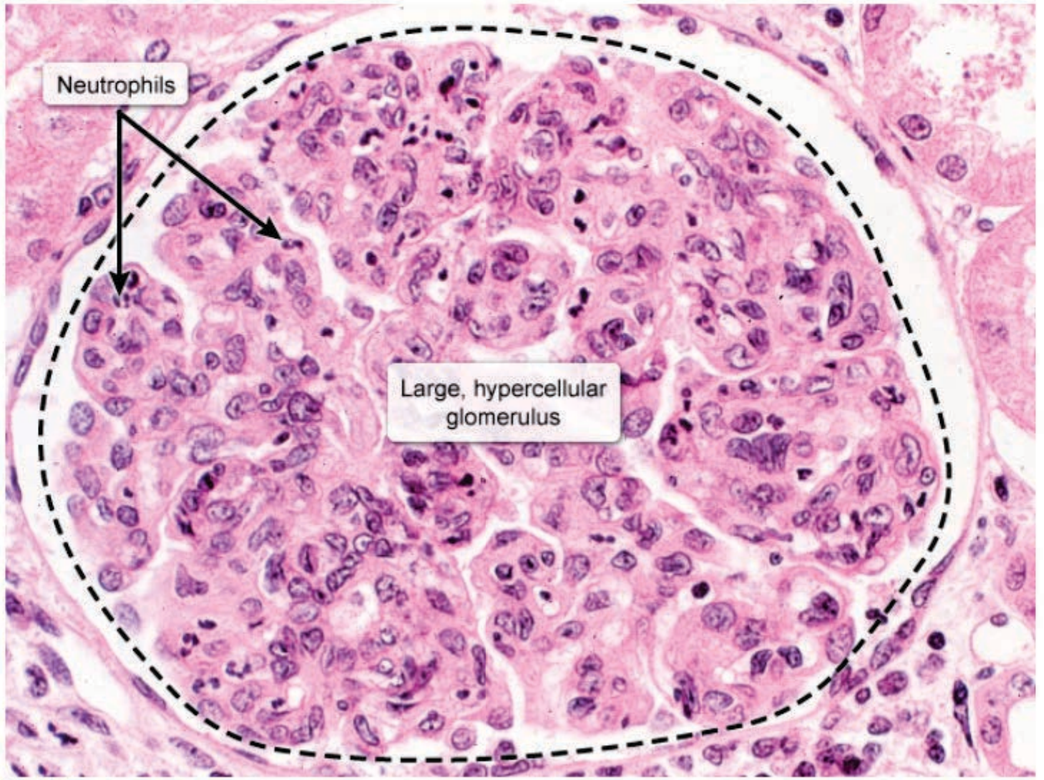
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Poststreptococcal glomerulonephritis



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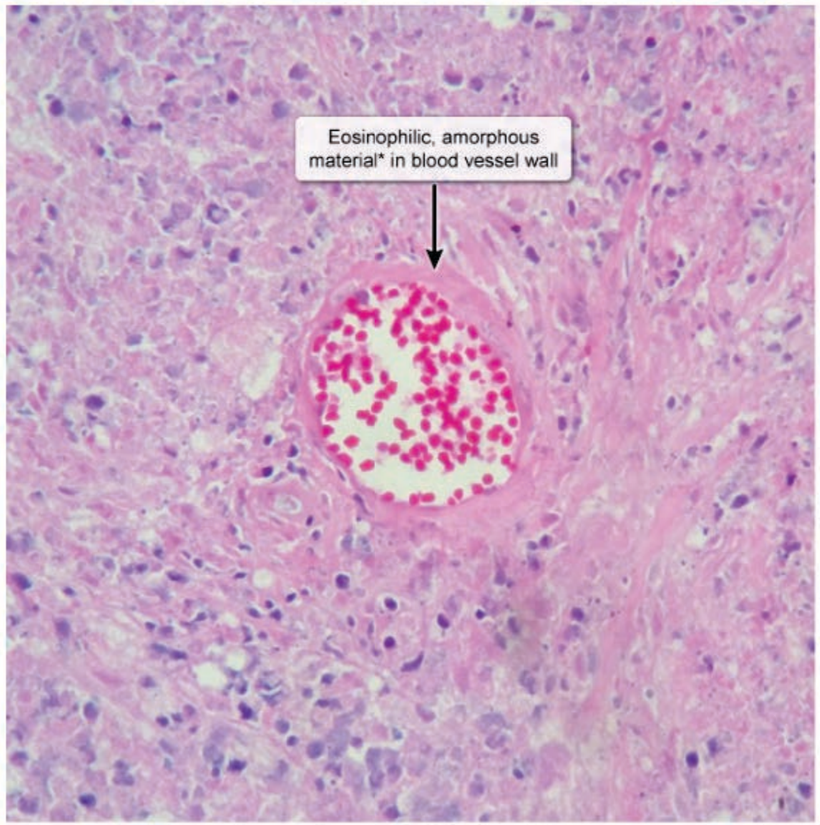
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Fibrinoid necrosis



*Fibrin deposition.

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Pathology Renal, Urinary Systems & Electrolytes Acute kidney injury

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Item 2 of 2

The patient's clinical condition gradually improves. On day 7 of hospitalization, his serum creatinine level is 1.1 mg/dL. Which of the following conditions would exhibit pathological kidney findings most similar to those observed in this patient?

- A. Diabetes mellitus
- ✗ B. Minimal change disease
- ✓ C. Severe rhabdomyolysis
- D. Systemic amyloidosis
- E. Systemic lupus erythematosus

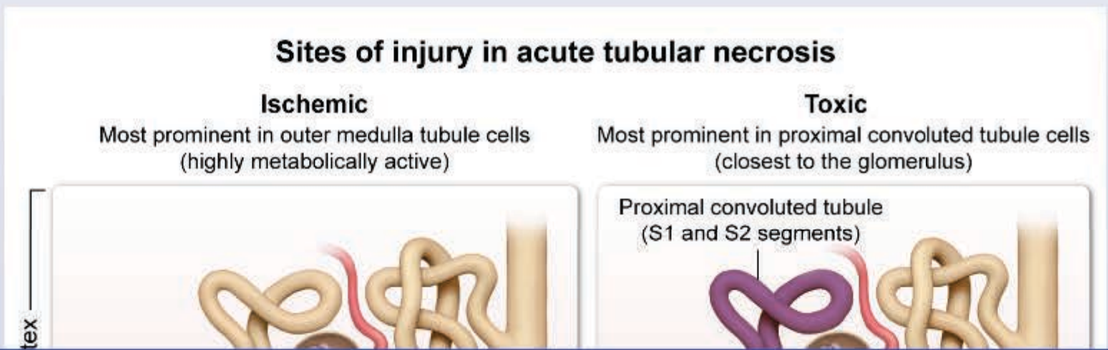
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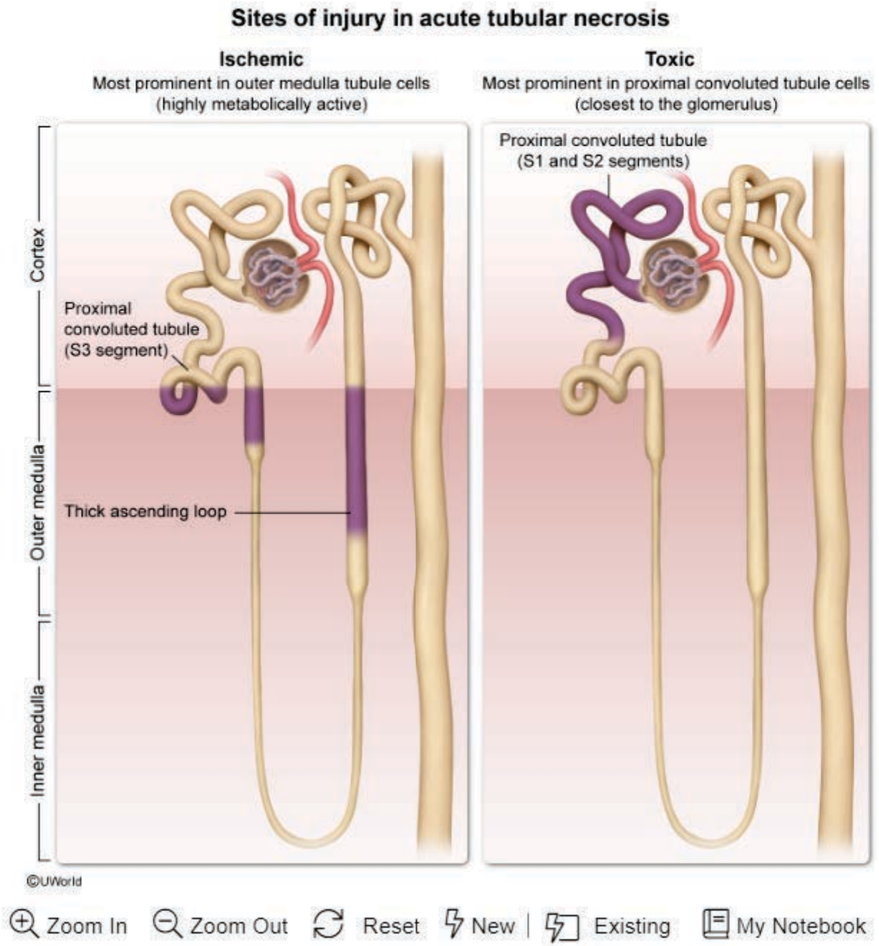
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Acute tubular necrosis (ATN) can be caused by ischemia (as in this patient) or **nephrotoxins**, which can be intrinsic (from within the body) or extrinsic (from outside the body). Intrinsic nephrotoxins include **myoglobin**—which is released from muscle cells during **rhabdomyolysis** (ie, muscle breakdown)—and uric acid. Extrinsic nephrotoxins include aminoglycosides, cisplatin, radiographic contrast dye, and heavy metals. Injury mechanisms in nephrotoxic ATN include direct cellular toxicity, intrarenal vasoconstriction, and tubular obstruction—depending upon the specific toxin.

Although the **histologic findings** in nephrotoxic ATN are **similar** to those seen in ischemic ATN, the pattern of injury is somewhat different. Ischemic ATN primarily affects the corticomedullary junction and outer medulla, whereas nephrotoxic ATN primary involves the **cortex**, particularly the S1 and S2 segments of the proximal convoluted tubule. With rhabdomyolysis, more proximal injury occurs because these segments are exposed first to the glomerular filtrate and endocytose much of the toxic myoglobin; distal tubular cells are relatively spared because the majority of the nephrotoxin has been reabsorbed.

(Choice A) Diabetic nephropathy results in nodular glomerulosclerosis, which is characterized by glomerular sclerosis, mesangial cell expansion, and deposition of immunoglobulins and other proteins in the renal glomerular arterioles (hyaline thickening). Nephrotic syndrome is the typical clinical presentation.

(Choice B) Minimal change disease is the most common cause of nephrotic syndrome in children. No abnormalities are seen on histology under light microscopy. Electron microscopy shows loss of podocyte foot processes.

(Choice D) Amyloidosis results in the deposition of amyloid protein in the kidney. The type of protein deposited is dependent on the cause of amyloidosis. Affected patients typically have either asymptomatic proteinuria or nephrotic syndrome.

(Choice E) Systemic lupus erythematosus causes lupus nephritis. It usually manifests with proteinuria and microscopic hematuria, and can progress to diffuse proliferative glomerulonephritis and end-stage renal disease.

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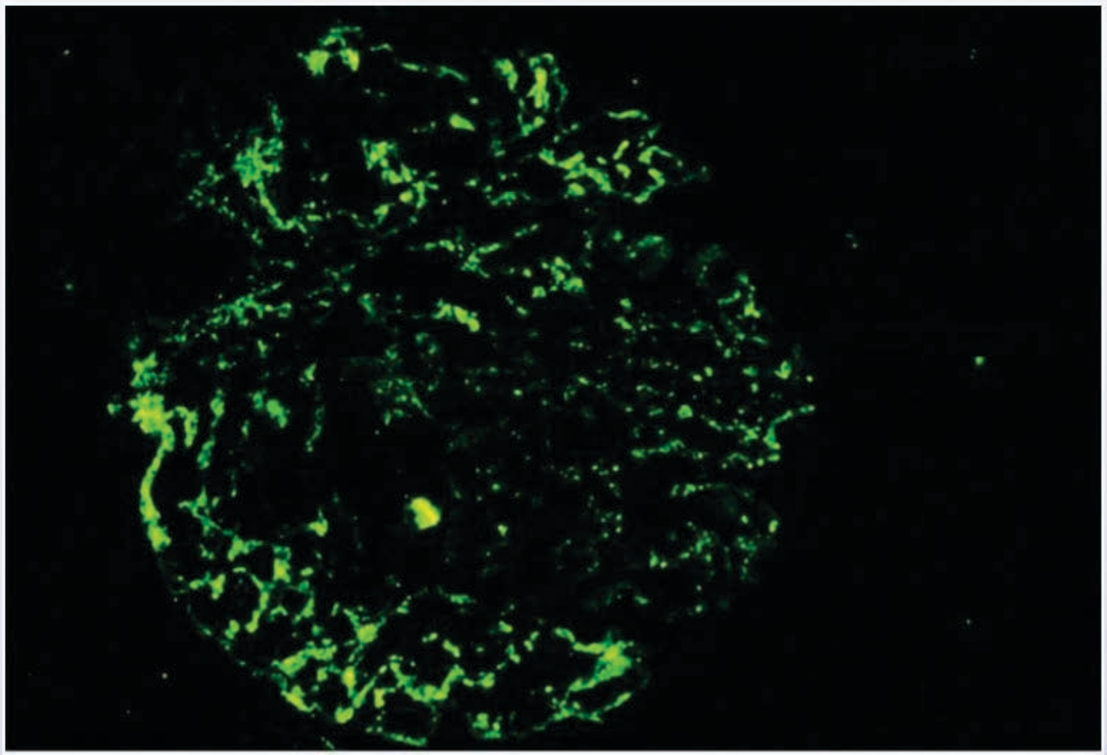
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Educational objective:
Acute tubular necrosis can be caused by ischemia or nephrotoxins. Potential nephrotoxins include myoglobin (ie, rhabdomyolysis), aminoglycosides, amphotericin B, radiographic contrast dye, and heavy metals.

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An 8-year-old boy is brought to the office due to acute facial puffiness. His mother reports that for the preceding 24 hours he has been easily fatigued and has had dark urine. The patient was treated for a skin infection 3 weeks ago but has no chronic medical conditions. Temperature is 36.1 C (97 F) and blood pressure is 140/94 mm Hg. Physical examination shows periorbital edema and mild pitting edema along the ankles. The remainder of the examination shows no abnormalities. A representative renal biopsy sample is shown in the image below:



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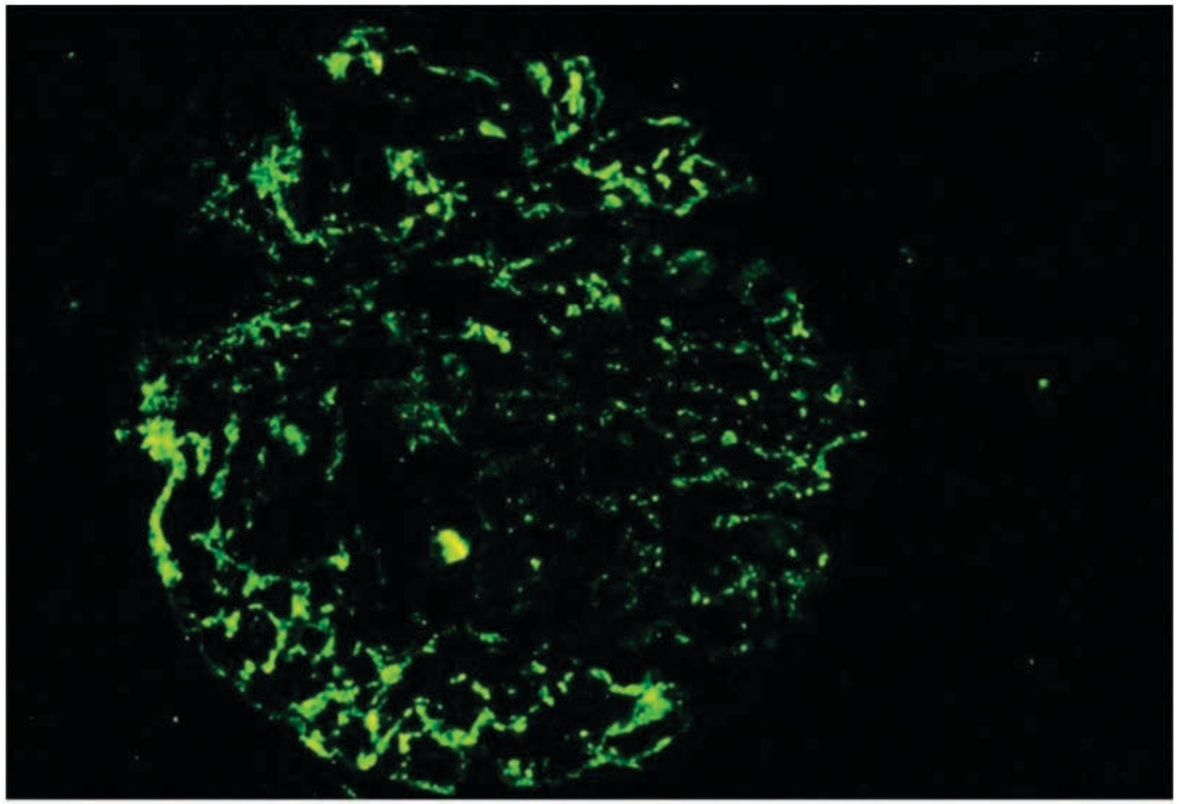
The fluorescent areas on the slide most likely indicate the presence of which of the following substances?

A Albumin

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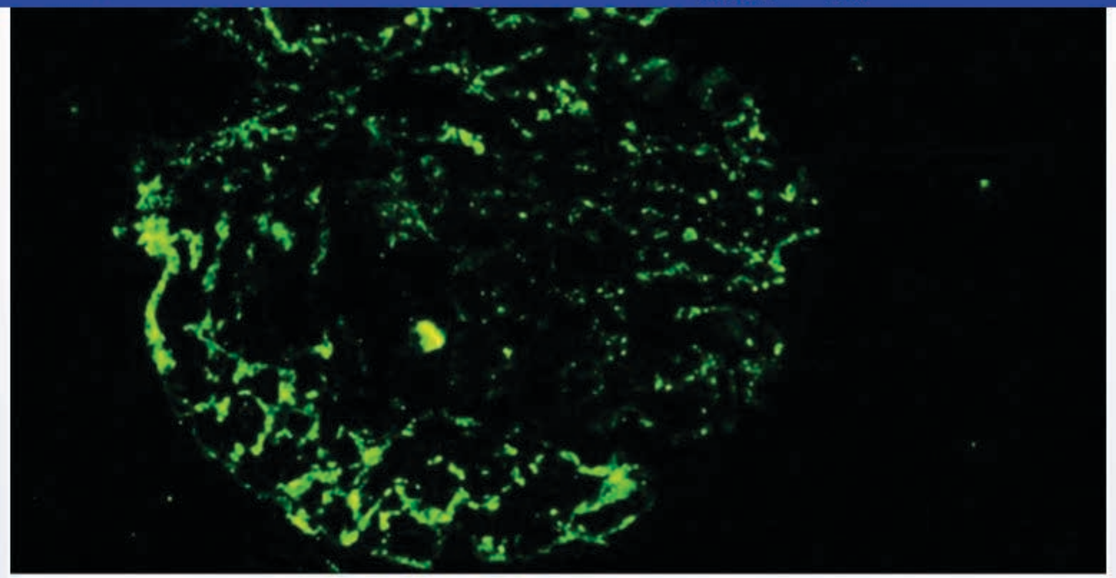
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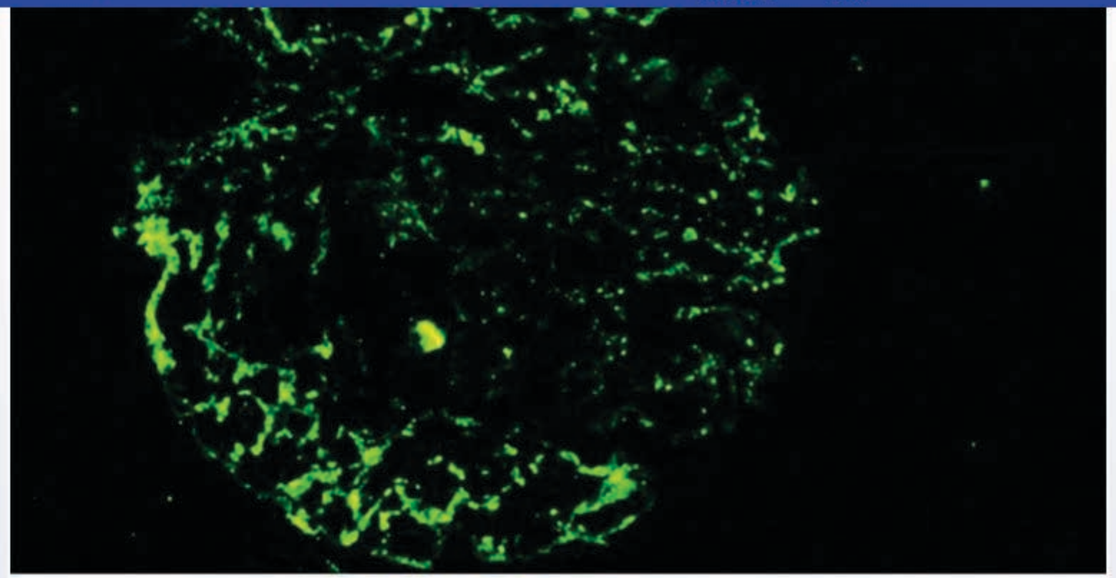
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The fluorescent areas on the slide most likely indicate the presence of which of the following substances?

- A. Albumin
- B. C1q
- C. C3
- D. Fibrin
- E. IgE
- F. M protein

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The fluorescent areas on the slide most likely indicate the presence of which of the following substances?

- A. Albumin (2%)
- B. C1q (3%)
- ✓ C. C3 (71%)
- D. Fibrin (2%)
- ✗ E. IgE (5%)
- F. M protein (13%)

Incorrect
Correct answer
C

71%
Answered correctly

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Explanation

This pediatric patient with nephritic syndrome (eg, periorbital edema, hematuria, hypertension) following a recent skin infection most likely has **poststreptococcal glomerulonephritis** (PSGN), the most common cause of pediatric nephritic syndrome. This typically occurs after exposure to strains of group A *Streptococcus* that produce nephritogenic antigens that can activate the alternate complement pathway. These combine with antibodies to form immune complexes, which deposit on the glomerular basement membrane (GBM) and induce complement activation and inflammation.

These immune complexes are visible on immunofluorescence microscopy as granular deposits of **IgG, IgM, and C3** on the GBM and mesangium. Because these particular immune complexes tend to activate complement via the alternate pathway, the deposits rarely contain C1q or C4 (classic complement pathway components) **(Choice B)**.

(Choice A) Disruption of the GBM in PSGN causes increased filtration of proteins such as albumin, which are lost in urine and do not deposit in the GBM. The loss of albumin results in decreased plasma oncotic pressure and subsequent peripheral edema.

(Choice D) Fibrin deposits in the Bowman space of the glomerulus are found in the crescents of rapidly progressive glomerulonephritis.

(Choice E) IgE deposits are sometimes seen in lupus nephritis and are confined to the capillary wall. They are associated with a poorer prognosis.

(Choice F) M protein is a component of the streptococcal cell wall that acts as an antiphagocytic virulence factor and stimulates antibody formation. The cross-reactivity of these antibodies to myosin within myocardial cells is likely responsible for rheumatic heart disease. However, M protein has not been isolated in the immune complexes in PSGN.

Educational objective:

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Educational objective:
Poststreptococcal glomerulonephritis occurs after exposure to strains of group A *Streptococcus* that produce nephritogenic antigens; antigen-antibody complexes deposit on the glomerular basement membrane and activate the alternate complement pathway. Immunofluorescence microscopy shows granular deposits of IgG, IgM, and C3 in the basement membranes and mesangium.

Histology | Renal, Urinary Systems & Electrolytes | Poststreptococcal Glomerulonephritis

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E. M protein (13%)

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Nephritic vs nephrotic syndrome		
	Nephritic	**Nephrotic**
Proteinuria	Mild	Significant (>3.5 g/day)
Serum albumin	Normal	Decreased
Edema	Mild	Significant
GFR	Decreased	Normal
Hypertension	Yes	No
Hematuria	Yes	No
Pyuria	Yes	No
Casts	RBC	Fatty or none

GFR = glomerular filtration rate; **RBC** = red blood cell.

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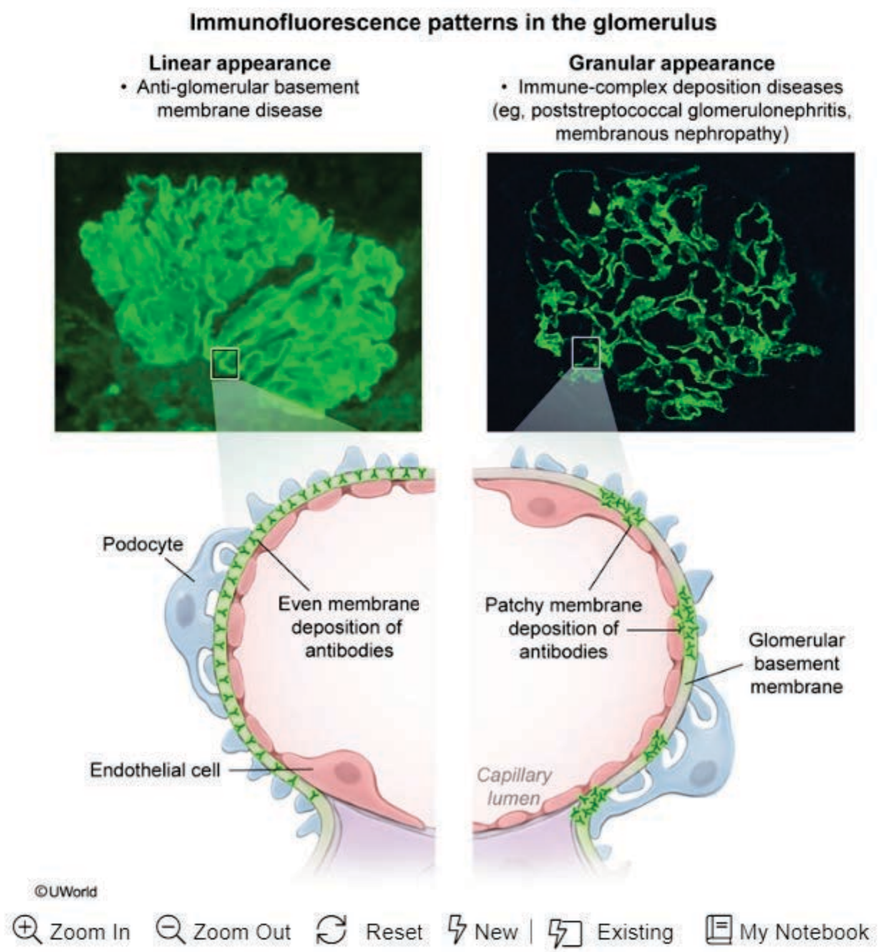
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E. M protein (13%)

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A 72-year-old man is brought to the emergency department due to diarrhea and vomiting for the last 24 hours. The patient's daughter states that he has been unable to take in much fluid during this time. He has hypertension treated with hydrochlorothiazide, which he has not taken since the onset of symptoms. Blood pressure is 90/60 mm Hg and pulse is 105/min. Examination shows dry mucous membranes. Urinalysis reveals concentrated urine with a specific gravity of 1.030. Which of the following changes in renal plasma flow (RPF), glomerular filtration rate (GFR), and filtration fraction (FF) are most likely to be present in this patient as compared with the normal state?

	RPF	GFR	FF
○ A.	↓↓	↓	↑
○ B.	↓↓	↓	↓
○ C.	↓↓	↑	↓
○ D.	↓	↑	↑
○ E.	↑	↑	↓

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	RPF	GFR	FF	
✓ A.	↓↓	↓	↑	(54%)
✗ B.	↓↓	↓	↓	(26%)
C.	↓↓	↑	↓	(5%)
D.	↓	↑	↑	(12%)
E.	↑	↑	↓	(1%)

Incorrect
Correct answer
A

54%
Answered correctly

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Explanation

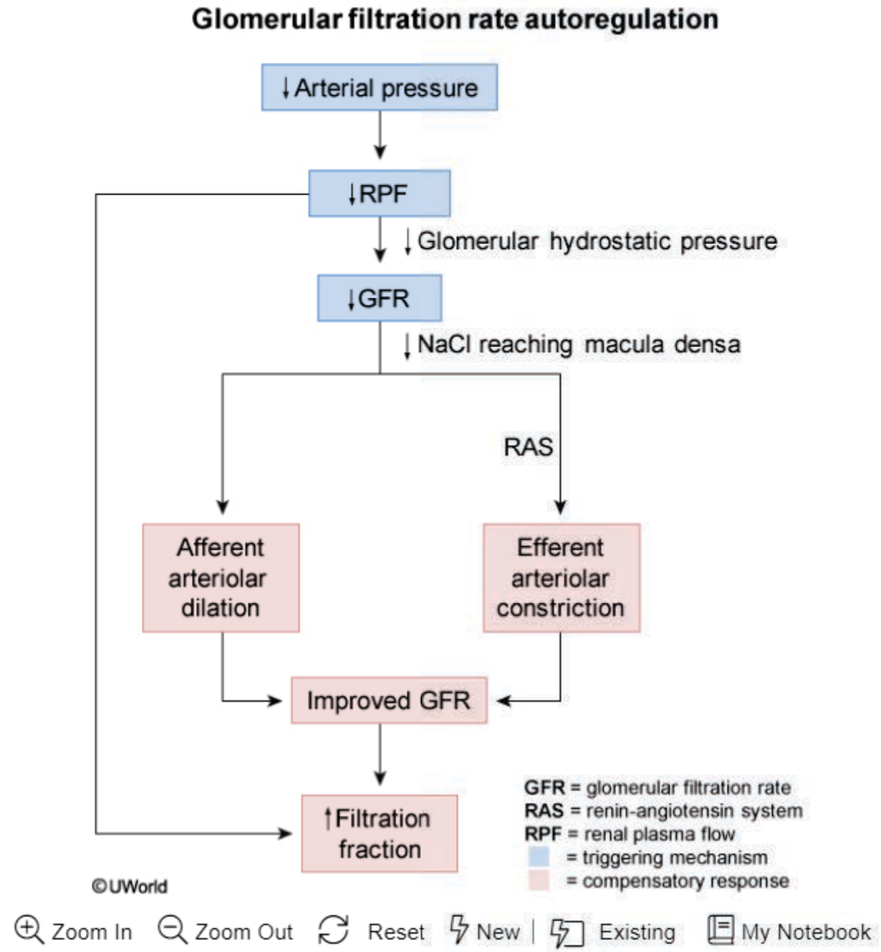
Glomerular filtration rate autoregulation

↓Arterial pressure

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E. ↑ ↑ ↓ (1%)

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Filtration of fluid through the glomeruli depends on the **renal plasma flow** (RPF) and the **glomerular filtration rate** (GFR). The GFR is the volume of fluid filtered from the renal glomerular capillaries into the Bowman capsule per unit of time. The RPF is the volume of plasma delivered to the kidney per unit of time. The **filtration fraction** (FF) is the ratio of GFR to RPF (FF = GFR/RPF). On average, approximately one-fifth of the plasma that passes through the glomerular capillaries is filtered into the Bowman capsule.

This patient is severely hypovolemic due to profuse diarrhea and vomiting. The decline in circulating blood volume is sensed by arterial and cardiac baroreceptors and triggers increased systemic arteriolar vasoconstriction. Renal vasoconstriction further lowers the RPF, which is already decreased due to the decline in circulating blood volume. Decreased RPF causes glomerular perfusion pressure to drop, lowering the GFR and reducing **distal tubule sodium delivery**. This stimulates secretion of renin and increased **angiotensin II** production. Angiotensin II preferentially constricts the efferent glomerular arteriole, which increases hydrostatic pressure in the glomerular capillaries to maintain GFR (**autoregulation**). Due to this compensatory mechanism, the decrease in GFR is less pronounced than the decrease in RPF, resulting in an increased FF **(Choices B, C, and E)**. As RPF continues to decline, increasing glomerular oncotic pressure will eventually overwhelm the compensatory increase in hydrostatic pressure, leading to a precipitous drop in GFR and subsequent renal failure.

(Choice D) Autoregulation improves but often cannot completely normalize the GFR in the setting of decreased renal perfusion pressure. If the net GFR were increased above normal, it would result in decreased renin formation and loss of the angiotensin II-driven arteriolar constriction required to maintain it.

Educational objective:
Hypovolemia results in a reduced renal plasma flow (RPF) and glomerular filtration rate (GFR). This leads to compensatory efferent arteriolar vasoconstriction, which raises the filtration fraction and maintains GFR at near-normal levels. As RPF continues to decline, increasing glomerular oncotic pressure will eventually overwhelm the compensatory increase in hydrostatic pressure, leading to a precipitous drop in GFR and renal failure.

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A 5-year-old boy is brought to the office by his parents due to bed-wetting. The patient has stayed dry during the day since age 3 but has continued to wet the bed 4 or 5 nights a week. He urinates approximately 5 times during the day; the urinary stream is continuous and strong. Bowel movements occur daily and are soft. The patient is otherwise healthy and takes no daily medications. Height and weight are tracking along the 75th percentile. Vital signs and examination are normal. Urinalysis is unremarkable. This patient's bed-wetting is most likely caused by which of the following?

- A. Bladder flaccidity
- B. Brain maturational delay
- C. Increased bladder capacity
- D. Osmotic diuresis
- E. Posterior urethral valves

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- A. Bladder flaccidity (15%)
- ✓ B. Brain maturational delay (52%)
- C. Increased bladder capacity (7%)
- D. Osmotic diuresis (14%)
- E. Posterior urethral valves (10%)

Correct

52% Answered correctly

04 secs Time Spent

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Explanation

Primary nocturnal enuresis	
Definition	• Nighttime urinary incontinence age ≥5 • No prior prolonged period of overnight dryness
	• Delayed maturation of bladder control

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Primary nocturnal enuresis	
Definition	• Nighttime urinary incontinence age ≥5 • No prior prolonged period of overnight dryness
Pathogenesis	• Delayed maturation of bladder control • ↑ Nocturnal urine output (eg, ↑ evening fluids, ↓ ADH) • ↓ Bladder capacity
Risk factors	• Family history • Boys age 5-8
Evaluation	• Urinalysis (to exclude other causes) • Voiding diary
ADH = antidiuretic hormone.	

This patient has **primary nocturnal enuresis**, defined as bed-wetting in a child age ≥5 who has never achieved a prolonged period of nighttime urinary continence.

The pathogenesis primarily involves a **maturational delay** in the **development of bladder control**. As neural pathways in the **brain** evolve over the first few years of life, voiding normally progresses from a primitive reflex to a purposeful action. This process of developing bladder control involves the following:

- Awareness of bladder filling
- Suppression of bladder contractions by the cerebral cortex
- Coordination of sphincter/detrusor function in the pontine micturition center

This process, and therefore toilet training, is typically complete by age 4 in most children. However, nighttime bladder control may be delayed until school age in others, leading to primary nocturnal enuresis. Patients with a

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This process, and therefore toilet training, is typically complete by age 4 in most children. However, nighttime bladder control may be delayed until school age in others, leading to primary nocturnal enuresis. Patients with a family history of nocturnal enuresis are at increased risk of delayed maturation.

In addition to delayed bladder control, the pathogenesis may also involve increased overnight urine output due to decreased antidiuretic hormone activity and/or excessive fluid consumption in the evenings. Reduced bladder capacity can also contribute **(Choice C)**.

(Choice A) Bladder flaccidity can occur in patients with impaired spinal cord signaling (eg, spina bifida causing neurogenic bladder). The sensation of bladder fullness is lost, which leads to both daytime and nighttime incontinence, incomplete emptying, and a weak urinary stream (eg, dribbling). In addition, other neurologic findings (eg, leg weakness) are usually expected with spinal cord lesions.

(Choice D) Osmotic diuresis is characterized by urinary excretion of excessive solute, such as glucose with diabetes mellitus. In addition to nocturnal enuresis, children with diabetes mellitus typically also have daytime polyuria and poor growth, which are not seen in this patient. Furthermore, glucosuria would be expected on urinalysis.

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- Suppression of bladder contractions by the cerebral cortex
- Coordination of sphincter/detrusor function in the pontine micturition center

This process, and therefore toilet training, is typically complete by age 4 in most children. However, nighttime bladder control may be delayed until school age in others, leading to primary nocturnal enuresis. Patients with a family history of nocturnal enuresis are at increased risk of delayed maturation.

In addition to delayed bladder control, the pathogenesis may also involve increased overnight urine output due to decreased antidiuretic hormone activity and/or excessive fluid consumption in the evenings. Reduced bladder capacity can also contribute **(Choice C)**.

(Choice A) Bladder flaccidity can occur in patients with impaired spinal cord signaling (eg, spina bifida causing neurogenic bladder). The sensation of bladder fullness is lost, which leads to both daytime and nighttime incontinence, incomplete emptying, and a weak urinary stream (eg, dribbling). In addition, other neurologic findings (eg, leg weakness) are usually expected with spinal cord lesions.

(Choice D) Osmotic diuresis is characterized by urinary excretion of excessive solute, such as glucose with diabetes mellitus. In addition to nocturnal enuresis, children with diabetes mellitus typically also have daytime polyuria and poor growth, which are not seen in this patient. Furthermore, glucosuria would be expected on urinalysis.

(Choice E) Posterior urethral valves are an anatomic abnormality that can cause nocturnal enuresis. However, patients also typically have daytime incontinence, obstructive symptoms (eg, weak stream), and recurrent urinary tract infections, none of which are seen in this child.

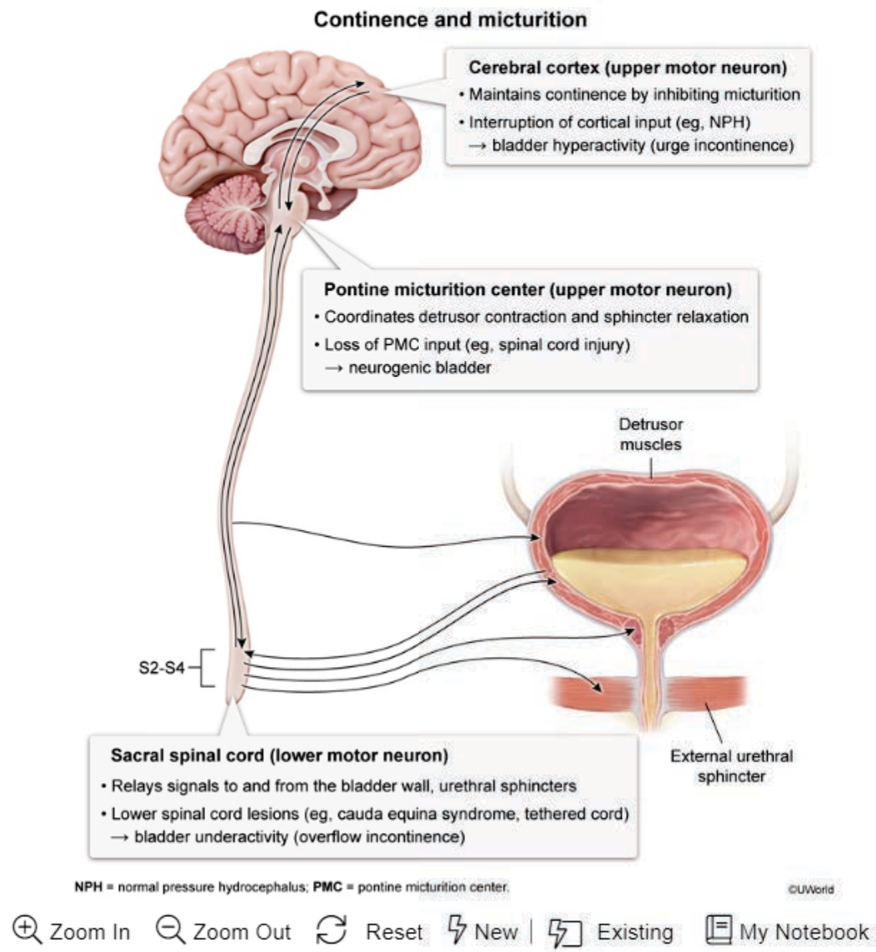
Educational objective:
Primary nocturnal enuresis (ie, bed-wetting at age ≥5 without prior nighttime urinary continence) is caused primarily by a brain maturational delay in the development of bladder control.

Physiology Renal, Urinary Systems & Electrolytes Enuresis

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- Suppression of bladder contractions by the cerebral cortex
- Coordination of sphincter/detrusor function in the pontine micturition center

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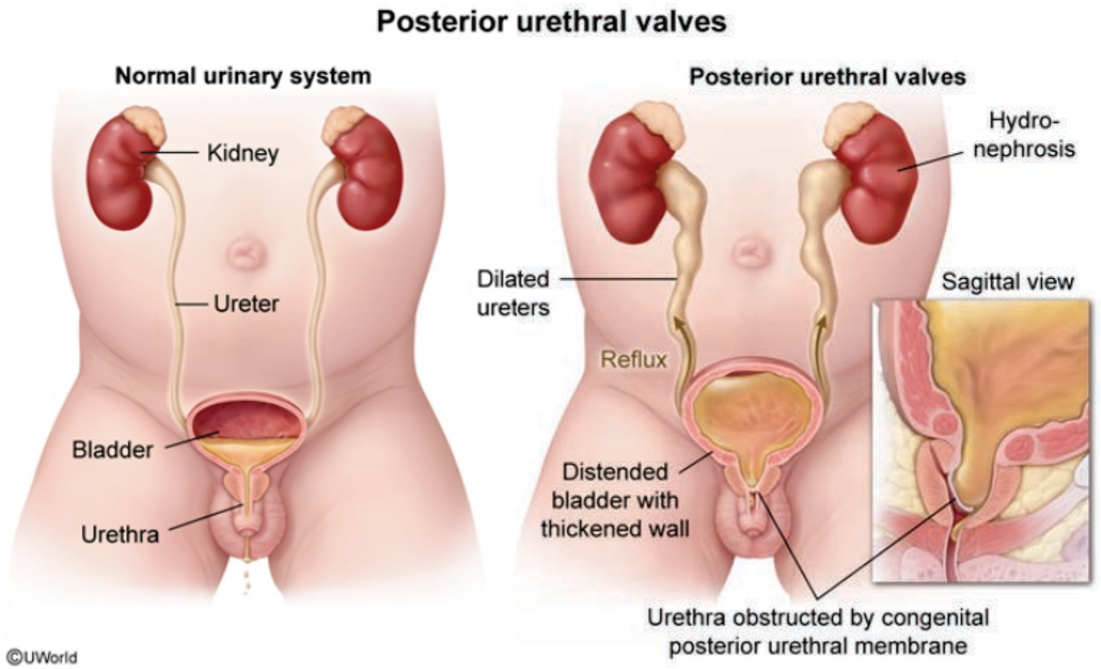
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Physiology Renal, Urinary Systems & Electrolytes Enuresis

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A 68-year-old man comes to the office due to intermittent, painless blood in his urine. He has no other symptoms. The patient uses transdermal testosterone for chronic hypogonadism and erectile dysfunction. He has smoked a pack of cigarettes daily for 40 years; he drinks 2 shots of vodka every day and 2 glasses of wine once a week. He works as an operations manager for a large beverage company and frequently travels to Mexico. Vital signs are within normal limits. Abdominal examination shows no abnormalities. On digital rectal examination, the prostate is smooth with no nodules. Urinalysis is positive for >50 red blood cells/hpf; there are no casts or dysmorphic blood cells. Urine cytology is positive for malignant cells. Renal ultrasonogram reveals normal kidneys. Which of the following is a major risk factor for this patient's current condition?

- A. Alcohol use
- B. Occupation
- C. Testosterone therapy
- D. Tobacco smoking
- E. Travel history

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- A. Alcohol use (2%)
- ✗ B. Occupation (2%)
- C. Testosterone therapy (2%)
- ✓ D. Tobacco smoking (89%)
- E. Travel history (3%)

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Correct answer
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89%
Answered correctly

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Explanation

Specific cancer risk factors			
Pancreas	• Tobacco smoke	**Renal**	• Tobacco smoke • Obesity

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Specific cancer risk factors			
Pancreas	• Tobacco smoke • Obesity	**Renal**	• Tobacco smoke • Obesity • Hypertension
Gastric	• Dietary nitrates • Alcohol & tobacco use • *Helicobacter pylori*	**Bladder**	• Tobacco smoke • Occupational exposures (rubber, plastics, aromatic amine–containing dyes, textiles, leather)
Liver	• Hepatitis B & C • Liver cirrhosis (any cause) • Hemochromatosis • Aflatoxin	**Breast**	• Early menarche • Late menopause • Nulliparity • *BRCA* mutations
Colorectal	• Hereditary CRC syndromes • Inflammatory bowel disease • Obesity • Charred or fried foods	**Prostate**	• Increasing age • African American
CRC = colorectal cancer.			

This patient has intermittent, **painless hematuria**. His positive urine cytology and negative imaging of the upper urinary tract suggest a **urothelial (transitional cell) cancer** in the **bladder**. The lesions in urothelial cancer can be visualized on cystoscopy as erythematous flat, nodular, or papillary lesions. On biopsy, the malignant cells are pleomorphic with hyperchromatic nuclei, an increased nucleus/cytoplasm ratio, disrupted orientation and polarity (in relation to the basal membrane), and frequent mitotic figures. Depth of invasion is important for staging;

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Urothelial cancer is most common in patients age >60, with men affected more than women. Major risk factors include **cigarette smoking** and occupational exposure to rubber, plastics, or aromatic amine-containing dyes (eg, used in textile and leather processing). Cyclophosphamide therapy (eg, for lymphoma, autoimmune disorders) also increases the risk.

(Choice A) Heavy alcohol intake is associated with increased risk of squamous cell carcinoma of the upper gastrointestinal tract (mouth, throat, esophagus) and hepatocellular carcinoma. The risk for bladder cancer is not significantly increased.

(Choice B) The carcinogens implicated in urothelial cancer are not commonly encountered in the food and beverage industry.

(Choice C) Testosterone therapy increases the risk for prostate cancer, which is often asymptomatic or discovered on evaluation for lower urinary tract voiding symptoms (eg, decreased force of stream, nocturia). Painless hematuria without voiding symptoms is more suggestive of bladder cancer.

(Choice E) *Schistosoma haematobium* is a trematode endemic to Africa and the Middle East that causes chronic infection in the bladder and increases the risk for a variety of bladder malignancies (including transitional cell and squamous cell carcinoma). This organism is not common in Mexico.

Educational objective:
Major risk factors for urothelial cancer of the bladder include age >60, cigarette smoking, and occupational exposure to rubber, plastics, or aromatic amine-containing dyes. Cyclophosphamide therapy also increases the

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Educational objective:
Major risk factors for urothelial cancer of the bladder include age >60, cigarette smoking, and occupational exposure to rubber, plastics, or aromatic amine-containing dyes. Cyclophosphamide therapy also increases the risk.

References

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A 68-year-old man comes to the emergency department due to lower abdominal pain and nausea. His symptoms started the prior evening, when he began to feel abdominal fullness and discomfort. This progressed to pain over the lower abdomen and constant nausea without vomiting. The patient last urinated >24 hours ago. He has had difficulty initiating urination and a feeling of incomplete voiding for the last year but avoided seeing a physician. Temperature is 36.7 C (98 F), blood pressure is 150/90 mm Hg, and pulse is 95/min. Physical examination shows suprapubic tenderness and fullness without guarding or rebound. Rectal examination reveals an enlarged, smooth prostate. Serum creatinine is 2.6 mg/dL and blood urea nitrogen is 22 mg/dL. A urinary catheter is placed, with immediate collection of 800 mL of urine and relief of the patient's symptoms. The following day, serum creatinine is improved. This patient's condition is associated with increased risk for which of the following?

- A. Bladder transitional cell carcinoma
- B. Glomerulonephritis
- C. Priapism
- D. Prostatic adenocarcinoma
- E. Urinary tract infection

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- A. Bladder transitional cell carcinoma (3%)
- ✗ B. Glomerulonephritis (4%)
- C. Priapism (1%)
- D. Prostatic adenocarcinoma (9%)
- ✓ E. Urinary tract infection (81%)

Incorrect
Correct answer
E

81%
Answered correctly

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Explanation

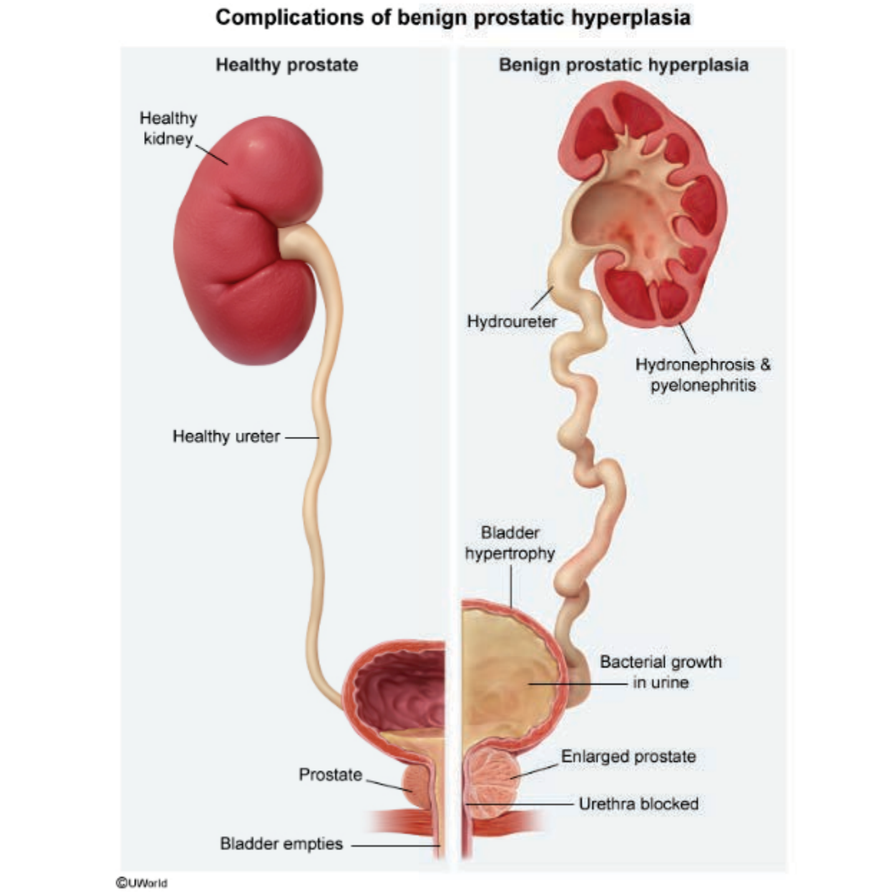
Complications of benign prostatic hyperplasia

Healthy prostate	Benign prostatic hyperplasia

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B. Glomerulonephritis (4%)

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This patient with progressive lower urinary tract symptoms and an enlarged prostate has **benign prostatic hyperplasia** (BPH). Bladder-outlet obstruction with **acute urinary retention** is a common complication of BPH and can occur with progressive disease or be triggered by medications that decrease bladder contractility (eg, sympathomimetic or anticholinergic medications).

Enlargement of the prostate (**static obstruction**) and contraction of prostatic smooth muscle (**dynamic obstruction**) compress the prostatic urethra, which increases the hydrostatic pressure required to overcome resistance to flow. As the bladder empties during micturition, urinary pressures diminish; if urinary pressure falls below the prostatic compressive pressure, urine flow stops, leaving a **residual volume** of urine in the bladder. Complete emptying of the bladder is a defense mechanism against urinary tract infection, but if the bladder does not empty completely, the residual urine can act as a growth medium for **pathogenic bacteria**. Other complications of BPH include bladder hypertrophy, hydroureter and hydronephrosis, and chronic kidney disease (obstructive uropathy).

(Choice A) Major risk factors for bladder transitional cell carcinoma include smoking and occupational exposure to aromatic amine-containing dyes. The risk is not significantly increased in patients with BPH.

(Choice B) Glomerulonephritis causes primary (intrarenal) azotemia and is not typically associated with BPH. Common causes of glomerulonephritis in adults include IgA nephropathy and membranoproliferative glomerulonephritis.

(Choice C) Priapism is prolonged erection of the penis that is not due to ongoing sexual stimulation. It may occur secondary to conditions that impair venous outflow from the penis (eg, sickle cell) or due to use of certain medications (eg, phosphodiesterase-5 inhibitors, trazodone). BPH does not increase the risk for priapism.

(Choice D) The risk for prostatic adenocarcinoma increases with age and is greatest in black patients and in individuals with a family history of prostate cancer. However, the risk is not appreciably increased in those with BPH or urinary obstruction.

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Enlargement of the prostate (**static obstruction**) and contraction of prostatic smooth muscle (**dynamic obstruction**) compress the prostatic urethra, which increases the hydrostatic pressure required to overcome resistance to flow. As the bladder empties during micturition, urinary pressures diminish; if urinary pressure falls below the prostatic compressive pressure, urine flow stops, leaving a **residual volume** of urine in the bladder. Complete emptying of the bladder is a defense mechanism against urinary tract infection, but if the bladder does not empty completely, the residual urine can act as a growth medium for **pathogenic bacteria**. Other complications of BPH include bladder hypertrophy, hydroureter and hydronephrosis, and chronic kidney disease (obstructive uropathy).

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Educational objective:
Benign prostatic hyperplasia can increase resistance to urine flow in the urethra and lead to incomplete bladder emptying during micturition. The residual urine can act as a growth medium for pathogenic bacteria and increase the risk for urinary tract infection.

References

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A 64-year-old man comes to the office due to several episodes of intermittent hematuria over the past 2 months. He has had no abdominal pain, burning on urination, or fever but has lost 4.5 kg (10 lb) since the onset of symptoms. The patient has smoked a pack of cigarettes daily for 30 years. Vital signs are within normal limits. The abdomen is soft, nontender, and nondistended. An enlarged and firm prostate is palpated on digital rectal examination. Serum calcium is 12.3 mg/dL. Urinalysis shows 30-40 red blood cells/hpf, negative protein, and no casts. A CT scan of the abdomen is shown below.

Which of the following is the most likely diagnosis?

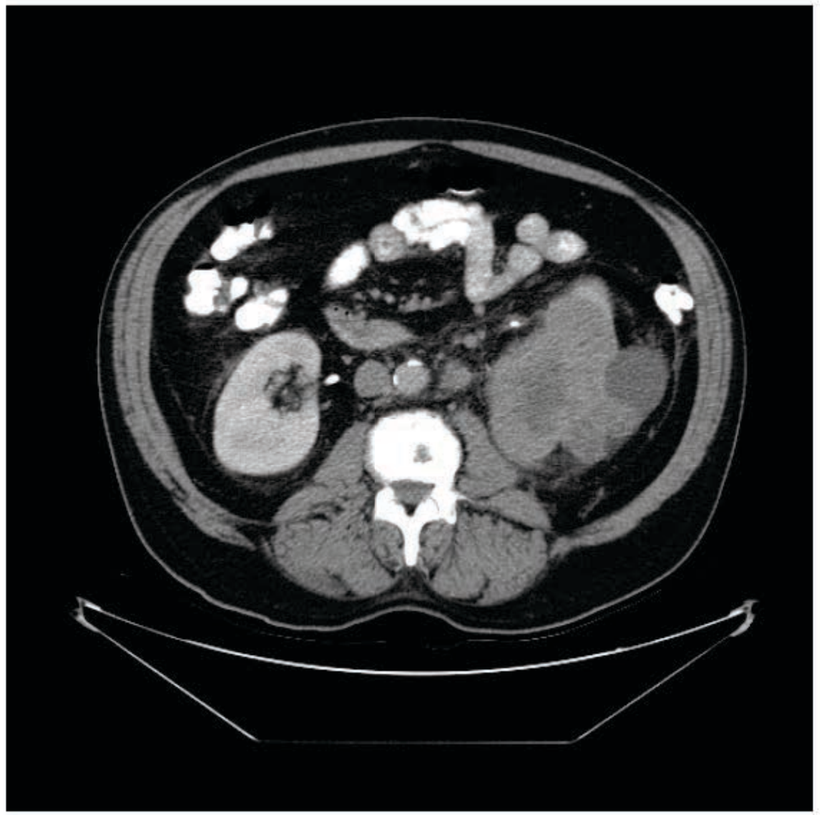
- A. Bladder cancer
- B. Pheochromocytoma
- C. Polycystic kidney disease
- D. Prostate cancer
- E. Renal cell carcinoma
- F. Ureterolithiasis

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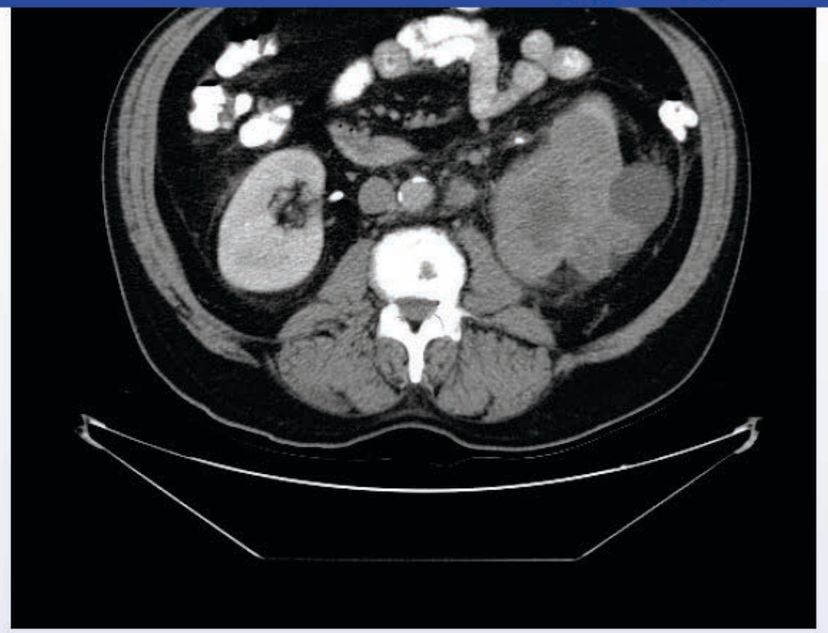
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Which of the following is the most likely diagnosis?

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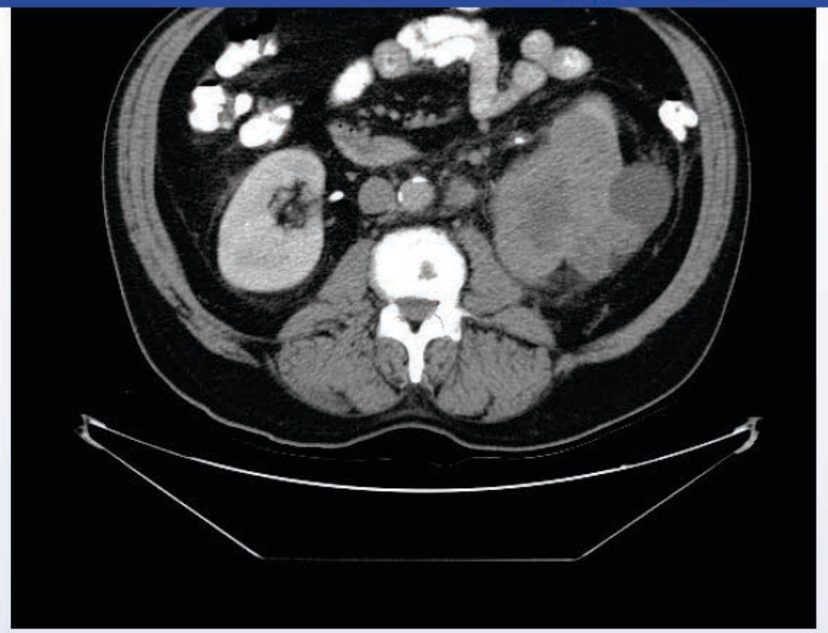


Which of the following is the most likely diagnosis?

- A. Bladder cancer
- B. Pheochromocytoma
- C. Polycystic kidney disease
- D. Prostate cancer
- E. Renal cell carcinoma
- F. Ureterolithiasis

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Which of the following is the most likely diagnosis?

- A. Bladder cancer (7%)
- ✗ B. Pheochromocytoma (0%)
- C. Polycystic kidney disease (8%)
- D. Prostate cancer (13%)
- ✓ E. Renal cell carcinoma (66%)
- F. Ureterolithiasis (3%)

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Correct answer
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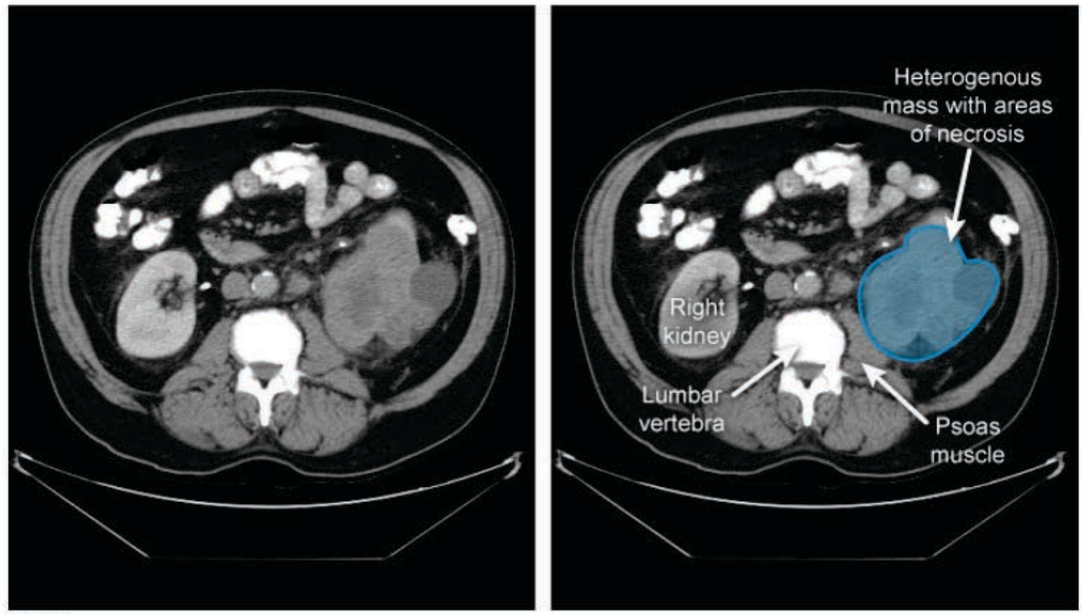
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Renal cell carcinoma



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cells. **Hypercalcemia** is frequently seen due to increased production of parathyroid hormone–related peptide or

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This patient with an extensive **smoking history,** 4.5-kg weight loss, painless hematuria, hypercalcemia, and renal mass likely has **renal cell carcinoma** (RCC). RCC originates in the renal cortex and accounts for up to 90% of primary renal tumors. It is often identified incidentally on radiographic imaging, and many individuals remain **asymptomatic** until the disease is relatively advanced. Hematuria is the most common symptom, and **painless hematuria** in an older adult should raise suspicion for a genitourinary malignancy. Patients may also have flank pain and a palpable abdominal mass at the time of presentation.

Paraneoplastic syndromes are common in RCC due to the secretion of biologically active substances by the tumor cells. **Hypercalcemia** is frequently seen due to increased production of parathyroid hormone–related peptide or overproduction of prostaglandins that promote bony resorption. **Erythrocytosis** due to ectopic erythropoietin production may also be seen.

(Choice A) Bladder cancer is another common cause of hematuria and weight loss; however, CT scan would demonstrate a bladder mass. This malignancy tends to metastasize to the liver, bones, and lungs. Although hypercalcemia may occur occasionally, it is more strongly associated with RCC.

(Choice B) Pheochromocytoma can cause severe, episodic hypertension associated with headaches, anxiety, palpitations, and sweating. A CT scan would reveal a suprarenal mass, and urine catecholamines and metanephrine would likely be elevated. Hematuria is not seen.

(Choice C) Polycystic kidney disease can cause hematuria; however, flank pain is common, and imaging would show bilateral renal cysts, not a unilateral mass. In addition, weight loss and hypercalcemia would be unexpected.

(Choice D) Prostate cancer typically presents with discrete nodules or asymmetric induration of the prostate on digital rectal examination. Diffuse, symmetric enlargement and firmness of the prostate are more suggestive of benign prostatic hyperplasia.

(Choice F) Ureterolithiasis is a common cause of hematuria, and patients with hypercalcemia from other causes (eg, hyperparathyroidism) are predisposed to stone formation. However, ureterolithiasis would not explain this patient's large, heterogeneous renal mass and unintended weight loss (which are highly suggestive of malignancy).

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Educational objective:
Classic signs and symptoms of renal cell carcinoma (RCC) include hematuria, an abdominal mass, flank pain, and weight loss. Hypercalcemia and erythrocytosis are common paraneoplastic syndromes associated with RCC.

Pathology	Renal, Urinary Systems & Electrolytes	Renal cell carcinoma
Subject	System	Topic

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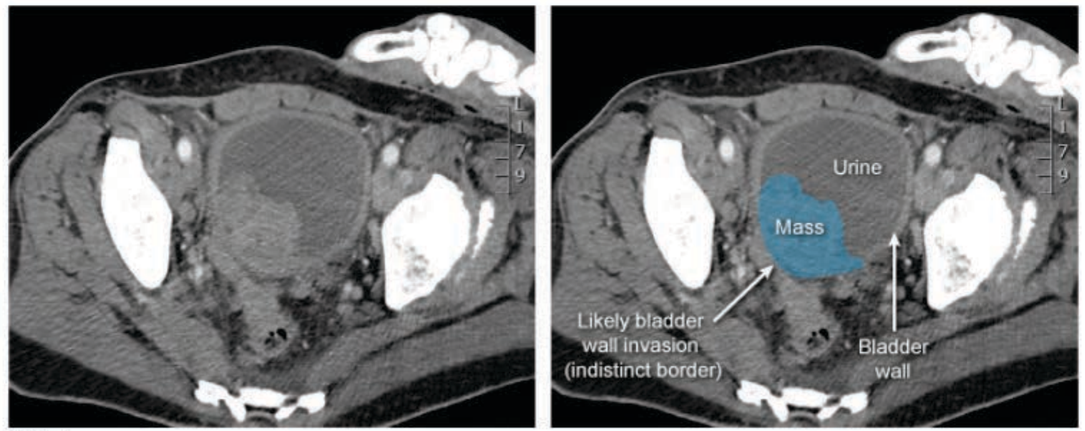
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benign prostatic hyperplasia.

Bladder mass

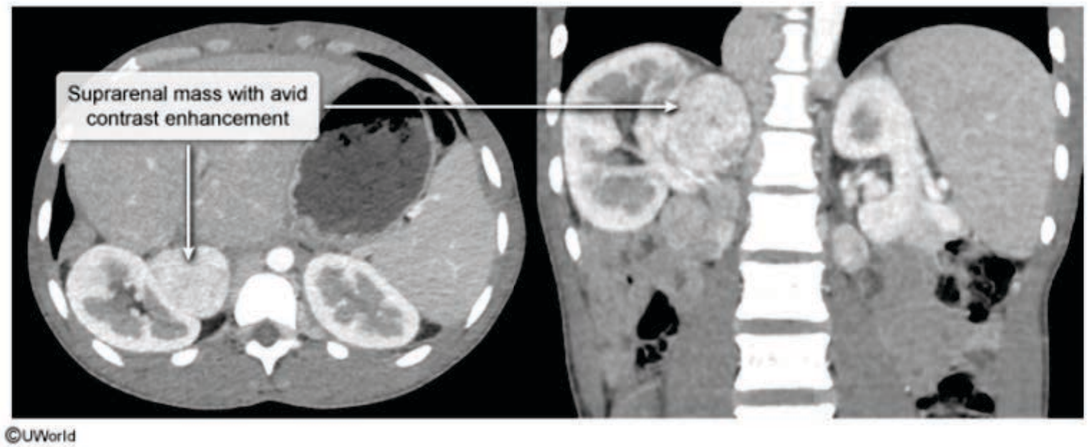


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This patient with an extensive **smoking history,** 4.5-kg weight loss, painless hematuria, hypercalcemia, and renal

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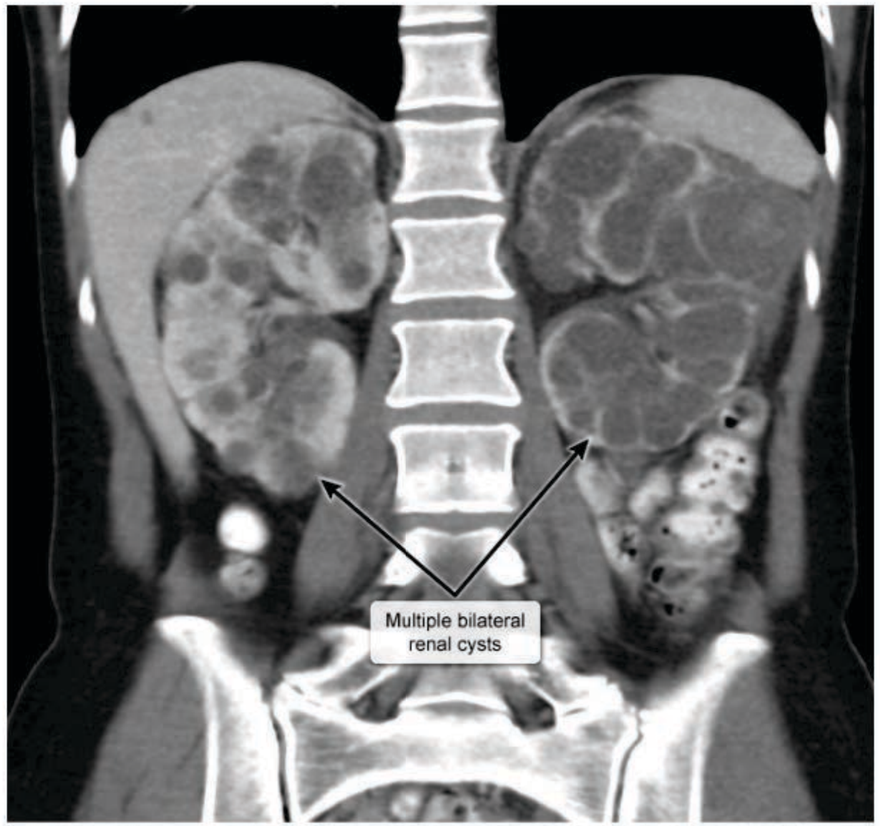
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Polycystic kidney disease



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A 20-year-old man is brought to the emergency department after a motor vehicle collision. Blood pressure is 130/84 mm Hg, pulse is 108/min, and respirations are 18/min. The airway is intact, and breath and heart sounds are normal. There is bruising across the central lower abdomen and the suprapubic area is tender to palpation. Chest x-ray and pelvic x-ray reveal no fractures. Bedside ultrasound shows intraperitoneal free fluid. Urine dipstick test is positive for blood. CT scan of the abdomen and pelvis is most likely to reveal which of the following injuries in this patient?

- A. Anterior bladder wall rupture
- B. Bladder dome rupture
- C. Bladder neck rupture
- D. Renal laceration
- E. Transection of anterior urethra

Submit

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A 20-year-old man is brought to the emergency department after a motor vehicle collision. Blood pressure is 130/84 mm Hg, pulse is 108/min, and respirations are 18/min. The airway is intact, and breath and heart sounds are normal. There is bruising across the central lower abdomen and the suprapubic area is tender to palpation. Chest x-ray and pelvic x-ray reveal no fractures. Bedside ultrasound shows intraperitoneal free fluid. Urine dipstick test is positive for blood. CT scan of the abdomen and pelvis is most likely to reveal which of the following injuries in this patient?

- A. Anterior bladder wall rupture (27%)
- ✓ B. Bladder dome rupture (45%)
- C. Bladder neck rupture (14%)
- D. Renal laceration (4%)
- E. Transection of anterior urethra (8%)

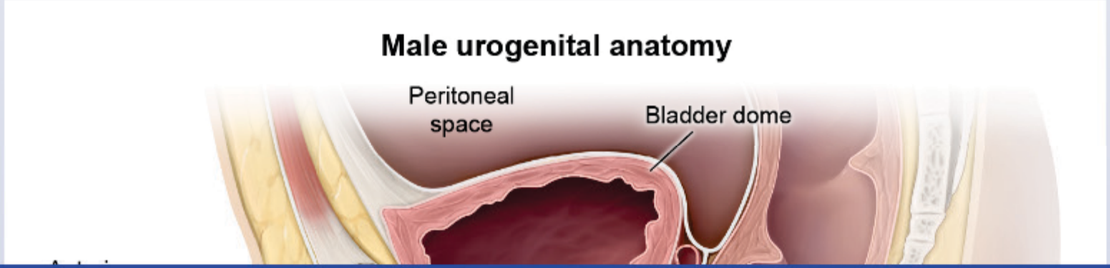
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Explanation

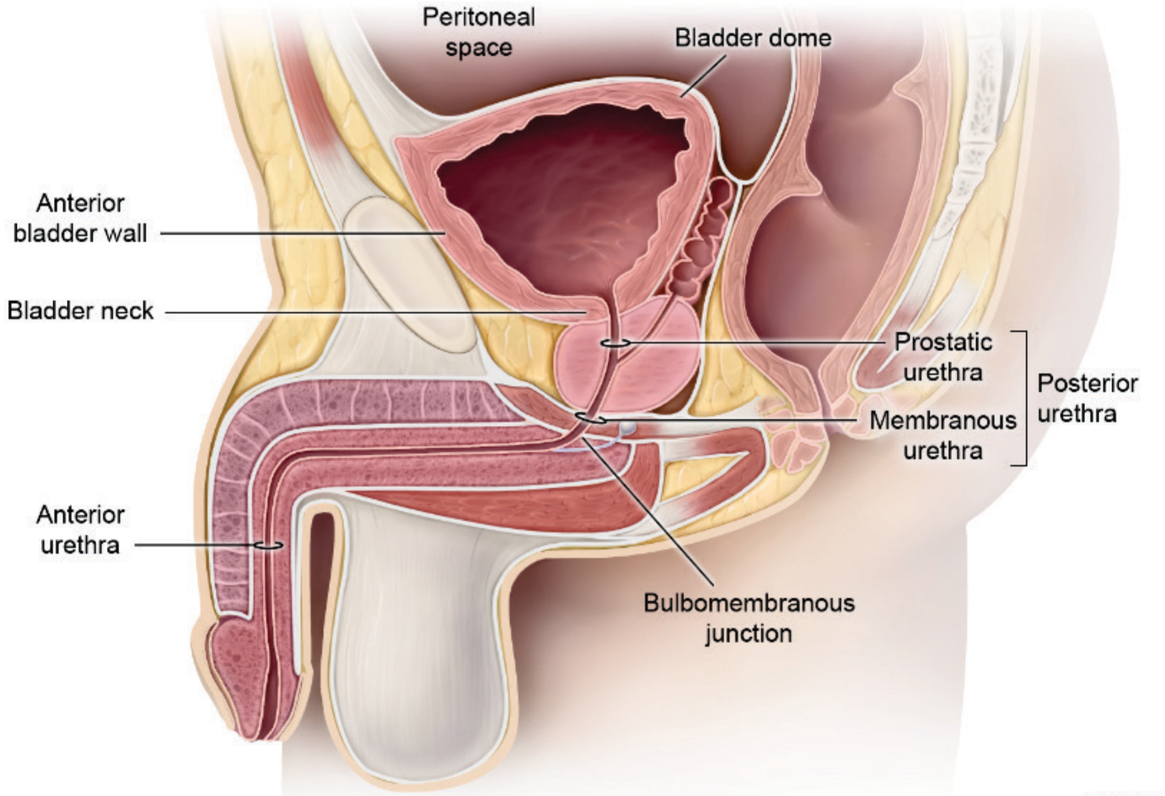


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E. Transection of anterior urethra (8%)

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Male urogenital anatomy



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This patient's **suprapubic tenderness** and **hematuria** (ie, urine dipstick test positive for blood) in the setting of blunt trauma are concerning for a bladder injury. The additional presence of intraperitoneal free fluid (possibly urine) is further suggestive of injury to the bladder dome.

The bladder is a hollow pelvic organ located just posterior to the pubic symphysis. Although the bladder is extraperitoneal, the **bladder dome** is covered by peritoneal lining and **extends into the peritoneal cavity** when distended with urine. Blunt lower abdominal trauma can abruptly increase intravesical pressure (especially when the bladder is full) and cause the bladder to **rupture** at the dome, where it is most distended and least supported by surrounding structures. As a result, urine is diverted from the urinary tract into the peritoneal cavity and can be seen on imaging as **intraperitoneal free fluid**. Peritonitis often does not develop acutely in these patients because urine typically does not contain pathogenic bacteria.

(Choices A and C) The anterior bladder wall and the bladder neck are extraperitoneal structures. Therefore, a rupture in these locations would lead to extraperitoneal extravasation of urine rather than intraperitoneal leakage of urine. In addition, such ruptures are almost always accompanied by pelvic fracture.

(Choice D) The kidney is a retroperitoneal structure. Therefore, renal laceration typically causes retroperitoneal bleeding and flank pain rather than intraperitoneal free fluid and suprapubic tenderness.

(Choice E) Urethral injuries can be categorized into anterior and posterior injuries. Anterior urethral injuries are commonly caused by direct penile trauma (eg, straddle injuries, penile fracture). Posterior urethral injuries are frequently associated with pelvic fracture and may (in cases of membranous transection) cause a high-riding prostate. Although urethral injury may cause blood at the urethral meatus and/or hematuria, it does not lead to intraperitoneal free fluid because the urethra is an extraperitoneal structure.

Educational objective:
The dome of the bladder rises into the peritoneal cavity when distended with urine. Blunt lower abdominal trauma can abruptly increase intravesical pressure and rupture the bladder dome, spilling urine into the intraperitoneal

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Educational objective:
The dome of the bladder rises into the peritoneal cavity when distended with urine. Blunt lower abdominal trauma can abruptly increase intravesical pressure and rupture the bladder dome, spilling urine into the intraperitoneal cavity.

References

- A contemporary review of adult bladder trauma.

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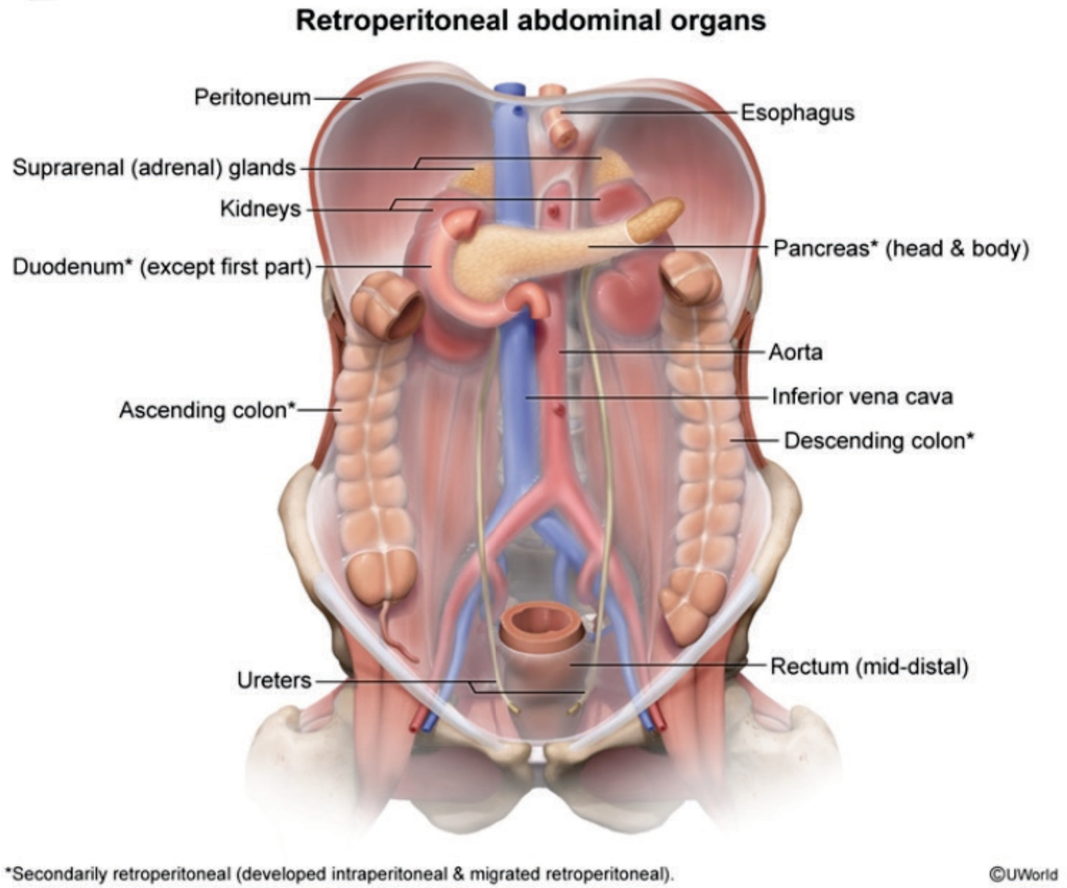
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can abruptly increase intravesical pressure and rupture the bladder dome, spilling urine into the intraperitoneal

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A 50-year-old man with polycystic kidney disease comes to the office due to constant, deep pain in his shoulders, arms, and legs. Medical history includes long-standing hypertension treated with ramipril. Blood pressure is 150/85 mm Hg and pulse is 78/min. Cardiopulmonary examination is normal. Abdominal examination shows large, palpable renal masses. Trace bilateral lower-extremity edema is present. Laboratory results from 2 years ago showed a blood urea nitrogen level of 25 mg/dL and a creatinine level of 2.3 mg/dL. Current laboratory results are as follows:

Sodium	136 mEq/L
Potassium	4.8 mEq/L
Chloride	104 mEq/L
Bicarbonate	22 mEq/L
Blood urea nitrogen	66 mg/dL
Creatinine	5.5 mg/dL
Calcium	7.5 mg/dL

Which of the following metabolic states is most likely present in this patient?

	Phosphate	Parathyroid Hormone	Calcitriol
A.	↓	↑	↑
B.	↑	↓	↑
C.	↑	↑	↓
D.	↓	↑	↓

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○ A.	↓	↑	↑
○ B.	↑	↓	↑
○ C.	↑	↑	↓
○ D.	↓	↑	↓
○ E.	↑	↓	↓

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Blood urea nitrogen	66 mg/dL
Creatinine	5.5 mg/dL
Calcium	7.5 mg/dL

Which of the following metabolic states is most likely present in this patient?

		Phosphate	Parathyroid Hormone	Calcitriol	
	A.	↓	↑	↑	(9%)
✗	B.	↑	↓	↑	(4%)
✓	C.	↑	↑	↓	(61%)
	D.	↓	↑	↓	(18%)
	E.	↑	↓	↓	(5%)

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Correct answer
C

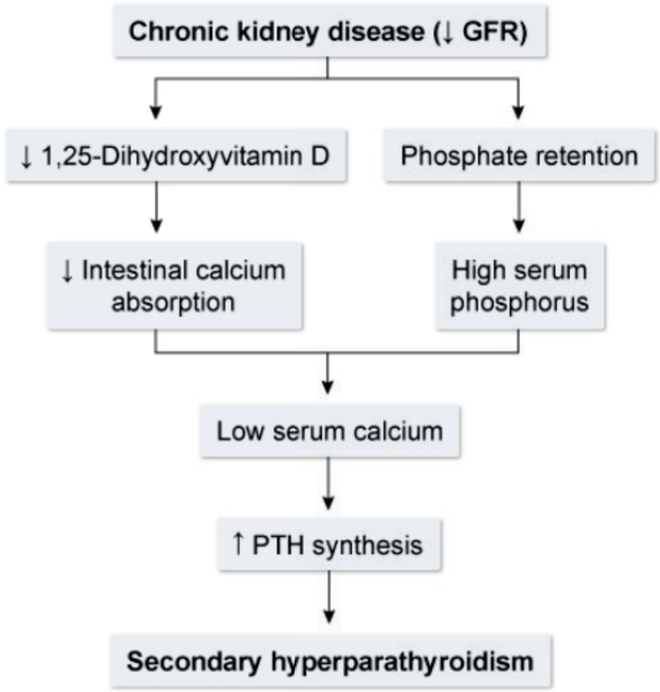
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GFR = glomerular filtration rate; **PTH** = parathyroid hormone.

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This patient's presentation is consistent with **metabolic bone disease** due to chronic kidney disease (CKD). CKD decreases the glomerular filtration rate (GFR), which decreases the filtered phosphate load and causes **elevated serum phosphate levels**. Hyperphosphatemia reduces serum free calcium and stimulates osteocytes and osteoclasts to release fibroblast growth factor-23 (FGF-23), a circulating peptide that decreases proximal tubule phosphate reabsorption. Elevated levels of phosphate and FGF-23 also **reduce calcitriol synthesis** by inhibiting the proximal tubular expression of 1-alpha-hydroxylase, resulting in decreased intestinal calcium and phosphate absorption. This worsens hypocalcemia but does not significantly improve hyperphosphatemia due to the low GFR, which is the limiting factor for phosphate excretion in patients with advanced CKD.

Hypocalcemia and hyperphosphatemia also **increase parathyroid hormone (PTH) secretion**, which stimulates osteoclasts to increase bone turnover. Long-term elevation in PTH (secondary hyperparathyroidism) can eventually lead to friable bones and **osteitis fibrosa**. Affected patients can develop weakness, **bone pain**, and fractures.

(Choice A) Primary hyperparathyroidism causes hypercalcemia and decreased serum phosphate due to inappropriately elevated PTH. Renal synthesis of calcitriol is also increased by PTH. In contrast, calcitriol levels remain low in patients with CKD due to the reduction in renal mass and the inhibitory effects of FGF-23 and phosphate.

(Choice B) Vitamin D toxicity raises calcitriol levels, which increases calcium and phosphate absorption causing hypercalcemia and hyperphosphatemia. Hypercalcemia inhibits PTH release, lowering serum PTH.

(Choice D) Vitamin D deficiency in patients with normally functioning kidneys decreases intestinal calcium and phosphate absorption, leading to lower serum phosphate and calcium levels. The resulting hypocalcemia stimulates PTH release from the parathyroid glands.

(Choice E) Primary hypoparathyroidism causes hypocalcemia and hyperphosphatemia due to decreased PTH. Calcitriol levels can also be low due to decreased PTH-mediated stimulation of renal 1-alpha-hydroxylase.

Educational objective:

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phosphate reabsorption. Elevated levels of phosphate and FGF-23 also **reduce calcitriol synthesis** by inhibiting the proximal tubular expression of 1-alpha-hydroxylase, resulting in decreased intestinal calcium and phosphate absorption. This worsens hypocalcemia but does not significantly improve hyperphosphatemia due to the low GFR, which is the limiting factor for phosphate excretion in patients with advanced CKD.

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(Choice E) Primary hypoparathyroidism causes hypocalcemia and hyperphosphatemia due to decreased PTH. Calcitriol levels can also be low due to decreased PTH-mediated stimulation of renal 1-alpha-hydroxylase.

Educational objective:
Chronic kidney disease causes disordered mineralization and bone metabolism that usually presents with hyperphosphatemia, secondary hyperparathyroidism, and decreased calcitriol levels. Patients can be asymptomatic or develop weakness, bone pain, and fractures.

References

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A 42-year-old man comes to the office due to a 2-week history of reddish-brown urine, fatigue, joint pain, and a lower extremity rash. The patient has no medical history, and family history is unremarkable. He has had multiple sexual partners and only uses protection intermittently. Temperature is 37.7 C (99.9 F), blood pressure is 146/94 mm Hg, and pulse is 75/min. Palpable purpura and pitting edema are present in bilateral lower extremities. Laboratory results are as follows:

Serum chemistry	
Creatinine	3.2 mg/dL
Liver function studies	
Aspartate aminotransferase (SGOT)	78 U/L
Alanine aminotransferase (SGPT)	96 U/L
Immunologic studies	
C3	low
C4	low
Urinalysis	
Protein	3+
White blood cells	2-3/hpf
Red blood cells	many/hpf
Casts	several RBC casts

Which of the following immunologic mechanisms is most likely responsible for this patient's renal injury?

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Liver function studies	
Aspartate aminotransferase (SGOT)	78 U/L
Alanine aminotransferase (SGPT)	96 U/L
Immunologic studies	
C3	low
C4	low
Urinalysis	
Protein	3+
White blood cells	2-3/hpf
Red blood cells	many/hpf
Casts	several RBC casts

Which of the following immunologic mechanisms is most likely responsible for this patient's renal injury?

- A. Antigen deposition in the glomerulus with subsequent immune complex formation
- B. Antibodies targeting intrinsic glomerular antigens with subsequent immune complex formation
- C. Antibodies causing neutrophil activation without significant immune complex deposition in the kidney
- D. Renal deposition of circulating immune complexes formed by endogenous antigens
- E. Renal deposition of circulating immune complexes formed by exogenous antigens

Submit

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Liver function studies	
Aspartate aminotransferase (SGOT)	78 U/L
Alanine aminotransferase (SGPT)	96 U/L
Immunologic studies	
C3	low
C4	low
Urinalysis	
Protein	3+
White blood cells	2-3/hpf
Red blood cells	many/hpf
Casts	several RBC casts

Which of the following immunologic mechanisms is most likely responsible for this patient's renal injury?

- A. Antigen deposition in the glomerulus with subsequent immune complex formation (13%)
- ✗ B. Antibodies targeting intrinsic glomerular antigens with subsequent immune complex formation (15%)
- C. Antibodies causing neutrophil activation without significant immune complex deposition in the kidney (6%)
- D. Renal deposition of circulating immune complexes formed by endogenous antigens (24%)
- ✓ E. Renal deposition of circulating immune complexes formed by exogenous antigens (40%)

Incorrect

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Immune mechanisms of glomerular injury*	
Immune complex formation within the glomerulus	• Intrinsic (fixed) glomerular antigens ◦ Type IV collagen: anti-GBM disease (GN) ◦ PLA2R: membranous nephropathy (NS) • Deposited ("planted") glomerular antigens ◦ Bacterial antigens: poststreptococcal GN ◦ Tumor antigens: membranous nephropathy (NS)
Preformed immune complex deposition from the circulation	• Endogenous antigens ◦ Galactose-deficient IgA: IgA nephropathy (GN) ◦ dsDNA: lupus nephritis (GN, sometimes NS) • Exogenous antigens ◦ Viral hepatitis C or B, HIV: immune complex MPGN ◦ Bacterial antigens: endocarditis-associated GN
Neutrophil activation: minimal (pauci-) immune complex deposition	• Neutrophil cytoplasmic antigens ◦ MPO/PR3 (ANCA-associated GN)

*Clinical picture determined by site of glomerular immune injury:

- **NS:** Injury to podocytes → isolated from inflammatory mediators in Bowman space/urinary side of GBM → proteinuria without inflammation
- **GN:** Injury to GBM, mesangial cells, or endothelial cells (either immune- or neutrophil-mediated) → exposed to inflammatory mediators/circulatory side of GBM → glomerular hematuria & red blood cell casts; variable proteinuria

ANCA = antineutrophil cytoplasmic antibody; **GBM** = glomerular basement membrane; **GN** = glomerulonephritis; **MPGN** = membranoproliferative glomerulonephritis; **MPO** = myeloperoxidase; **NS** = nephrotic syndrome; **PLA2R** = phospholipase A2 receptor; **PR3** = proteinase 3.

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This patient's acute kidney injury (eg, elevated creatinine), proteinuria, hypertension, and glomerular hematuria (eg, **red cell casts**) are indicative of **glomerulonephritis** (GN). GN is commonly a manifestation of **small vessel vasculitis** (SVV), which usually has associated systemic symptoms (eg, **fever**, fatigue). GN due to SVV is immune mediated by 3 possible mechanisms:

- Antibodies targeting antigens in the glomerulus (intrinsic or deposited) with immune complex (IC) formation in the kidney
- Preformed circulating ICs targeting endogenous or exogenous antigens with subsequent kidney deposition
- Antibodies targeting neutrophil antigens causing neutrophil activation without significant IC deposition

Several features of this patient's presentation suggest **GN/SVV due to hepatitis C virus** (HCV). Evidence for HCV infection includes multiple sexual partners and elevated aminotransferases. HCV-infected patients often produce cryoglobulins against **exogenous** HCV antigens that form **circulating ICs**, which activate complement, causing hypocomplementemia. These circulating ICs can deposit in small vessels ("cryoglobulinemic vasculitis") affecting the kidney (eg, membranoproliferative GN), skin (eg, palpable purpura), and joints (eg, arthralgias).

(Choices A and B) Antibodies targeting glomerular antigens, whether intrinsic (eg, membranous nephropathy) or deposited (eg, poststreptococcal GN), form ICs within the kidney; this typically results in *renal-limited disease*. Anti-GBM disease is an exception because the antibodies are directed against type IV collagen, which is also present in alveoli resulting in alveolar hemorrhage. This patient's fever, arthralgias, and rash indicate a *systemic process* characteristic of circulating immune complex deposition.

(Choice C) Antibodies targeting neutrophil antigens (myeloperoxidase, proteinase 3) can activate neutrophils, causing ANCA-associated GN and SVV (without significant IC deposition). Although the skin and joints can be affected, the respiratory tract and nerves are typically involved, and hypocomplementemia is unusual.

(Choice D) Preformed circulating ICs against endogenous antigens are the cause of IgA nephropathy and lupus nephritis. IgA nephropathy is more common in children following upper respiratory infections; serum complement

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(Choice D) Preformed circulating ICs against endogenous antigens are the cause of IgA nephropathy and lupus nephritis. IgA nephropathy is more common in children following upper respiratory infections; serum complement is usually normal because IgA fixes complement poorly. Lupus nephritis is associated with arthralgia, vasculitis, and hypocomplementemia; however, this patient's presentation (eg, male sex, sexual risk factors) is more suggestive of underlying hepatitis C infection.

Educational objective:
Immune glomerular injury results from immune complexes (ICs) or neutrophil activation. IC formation in the kidney typically produces renal-limited disease (except anti–glomerular basement membrane disease). Preformed circulating IC deposition is usually associated with small vessel vasculitis and hypocomplementemia.

Pathology Renal, Urinary Systems & Electrolytes Glomerular disorders

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A 57-year-old man comes to the office for a follow-up appointment. He has a history of systolic heart failure, which has been managed with appropriate medical therapy. The patient experiences significant functional impairment at baseline and is able to walk only short distances. His most recent echocardiogram revealed a left ventricular ejection fraction of 30% (normal ≥55%). The physician decides to add spironolactone to the treatment regimen. The addition of this medication is most likely to cause a decrease in which of the following?

- A. Hydrogen ion generation by the proximal convoluted tubule
- B. Hydrogen ion secretion from the collecting duct
- C. $Na^+/K^+/2Cl^-$ cotransport in the thick ascending limb
- D. Proximal convoluted tubule brush border transport capacity
- E. Urea reabsorption in the collecting duct

Submit

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- A. Hydrogen ion generation by the proximal convoluted tubule (2%)
- ✓ B. Hydrogen ion secretion from the collecting duct (79%)
- C. $Na^+/K^+/2Cl^-$ cotransport in the thick ascending limb (5%)
- D. Proximal convoluted tubule brush border transport capacity (1%)
- E. Urea reabsorption in the collecting duct (10%)

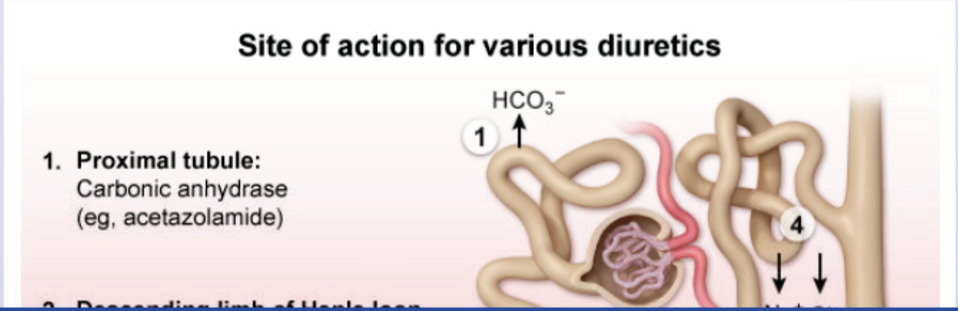
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79% Answered correctly

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Explanation

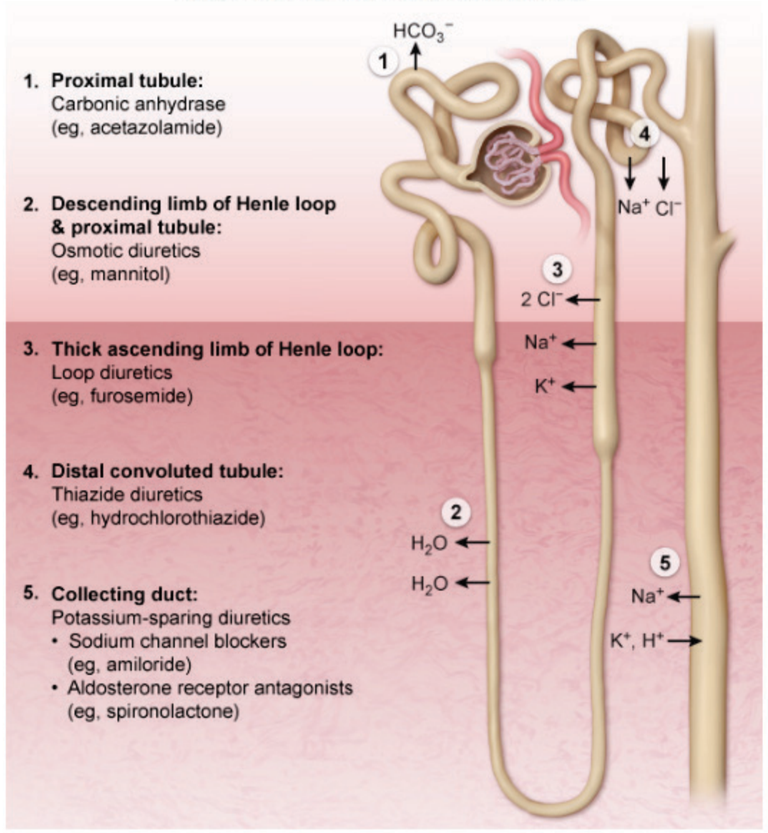


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A 57-year-old man comes to the office for a follow-up appointment. He has a history of systolic heart failure, which has base ejec The

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Site of action for various diuretics



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Aldosterone is a mineralocorticoid produced by the adrenal zona glomerulosa in response to hypotension and reduced renal blood flow (renin-angiotensin-aldosterone system). Hyperkalemia can also stimulate aldosterone secretion.

Aldosterone acts primarily in the collecting duct, where it increases the number of basolateral Na^+/K^+-ATPase pumps and apical sodium channels on principal cells, increasing sodium and water reabsorption. It also promotes **potassium and hydrogen ion secretion** from the principal and intercalated cells, respectively.

Aldosterone receptor antagonists (eg, spironolactone, eplerenone) inhibit the effects of aldosterone and reduce sodium reabsorption and potassium and hydrogen ion secretion in the collecting duct. Benefits include enhanced diuresis and lower blood pressure. Adverse effects of these medications include hyperkalemia, hyponatremia, metabolic acidosis, and gynecomastia (with spironolactone, which also inhibits the testosterone receptor).

(Choice A) Intracellular carbonic anhydrase in the proximal tubule generates H^+, which is secreted into tubular fluid and used by brush border carbonic anhydrase to help resorb filtered HCO_3^-. Carbonic anhydrase inhibitors (eg, acetazolamide) suppress both membrane-bound and cytoplasmic forms.

(Choice C) The $Na^+/K^+/2Cl^-$ cotransporter in the thick ascending limb is the target of loop diuretics (eg, furosemide), which cause brisk diuresis by inhibiting solute reabsorption.

(Choice D) The microvilli-covered epithelial cells (brush border) of the proximal convoluted tubule have a high capacity for reabsorption of electrolytes, glucose, and amino acids. Isosmotic water reabsorption follows passively. Reabsorption in this segment of the nephron is not affected by aldosterone, but is enhanced by angiotensin II.

(Choice E) In addition to increasing the water permeability of the collecting duct, vasopressin (antidiuretic hormone) raises urea reabsorption by increasing the number of cell surface urea transporters. This strengthens the corticomedullary interstitial osmotic gradient, facilitating water reabsorption and increasing urine concentration.

Educational objective:

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potassium and hydrogen ion secretion from the principal and intercalated cells, respectively.

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Educational objective:
Aldosterone acts on the principal and intercalated cells of the renal collecting tubules to increase resorption of sodium and water and increase excretion of potassium and hydrogen ions. Aldosterone receptor antagonists (eg, spironolactone, eplerenone) inhibit these effects.

Pharmacology	Renal, Urinary Systems & Electrolytes	Aldosterone antagonists
Subject	System	Topic

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Potassium-sparing diuretics
• Sodium channel blockers

K^+, H^+ →

Exhibit Display

Adrenal cortical structure & function

Principal stimulatory hormone	Adrenal layer	Principal secreted hormone	Physiologic effect
Angiotensin II	Zona glomerulosa	Aldosterone	↑ Blood volume
ACTH	Zona fasciculata	Cortisol	↑ Vascular tone ↑ Blood glucose
ACTH	Zona reticularis	Androgens	Libido & pubic hair in women
	Medulla		

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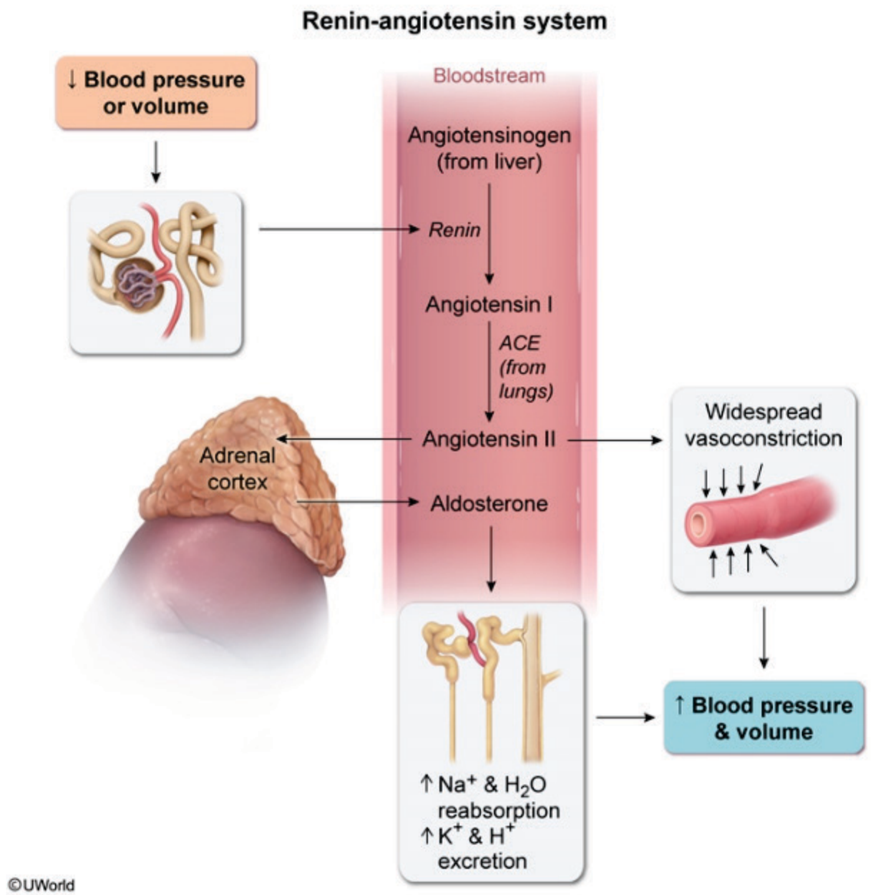
capacity for reabsorption of electrolytes, glucose, and amino acids. Isosmotic water reabsorption follows

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Potassium-sparing diuretics
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K^+, H^+ →

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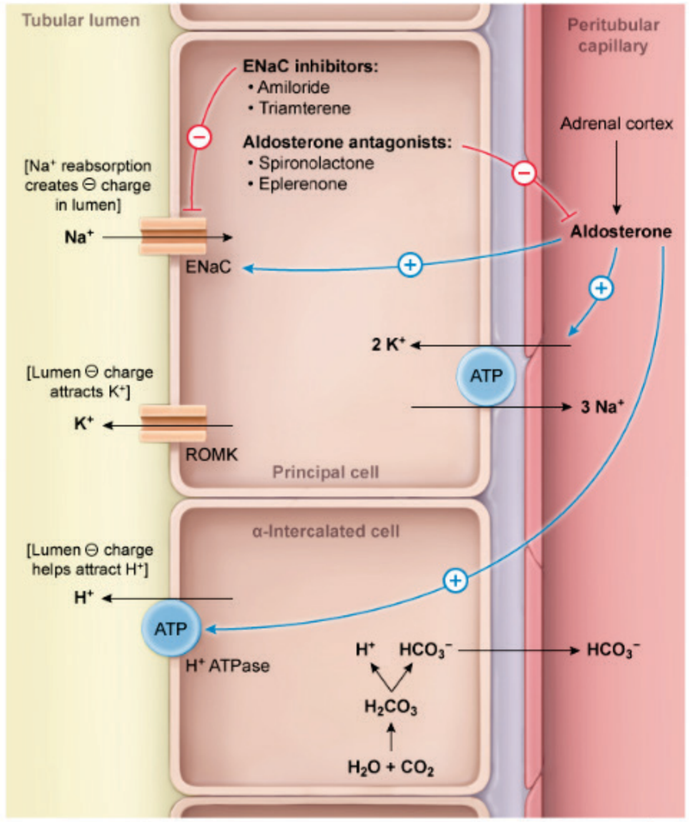
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Potassium-sparing diuretics
• Sodium channel blockers

K^+, H^+ →

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Action of aldosterone in the collecting duct of the nephron



ENaC = epithelial sodium channel; **ROMK** = renal outer medullary potassium channel. ©UWorld

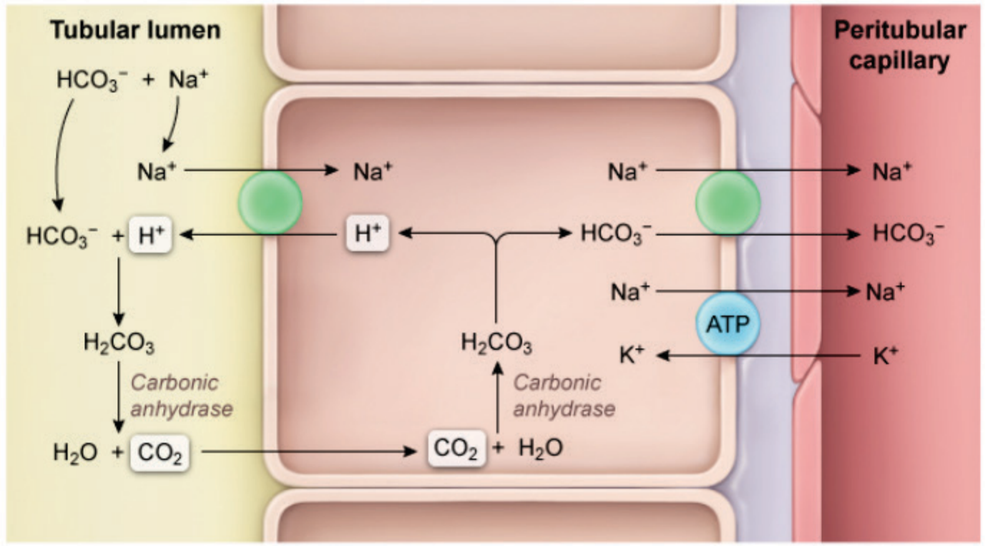
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capacity for reabsorption of electrolytes, glucose, and amino acids. Isosmotic water reabsorption follows

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Proximal tubule bicarbonate reabsorption



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(Choice E) In addition to increasing the water permeability of the collecting duct, vasopressin (antidiuretic

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A 43-year-old woman with borderline personality disorder is brought to the emergency department after taking an undetermined number of pills. She is lethargic but arousable. She refuses to answer questions. Blood pressure is 110/60 mm Hg and heart rate is 120/min and regular. Laboratory results are as follows:

Serum chemistry	
Sodium	139 mEq/L
Potassium	3.3 mEq/L
Chloride	98 mEq/L
Bicarbonate	13 mEq/L
Arterial blood gases on room air	
pH	7.46
$PaCO_2$	19 mm Hg
PaO_2	96 mm Hg
Oxygen saturation	99%

Which of the following best describes this patient's acid-base disturbance?

- A. Metabolic acidosis and metabolic alkalosis
- B. Metabolic acidosis and respiratory acidosis
- C. Metabolic acidosis and respiratory alkalosis
- D. Metabolic alkalosis and respiratory acidosis
- E. Metabolic alkalosis and respiratory alkalosis

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$PaCO_2$	19 mm Hg
PaO_2	96 mm Hg
Oxygen saturation	99%

Which of the following best describes this patient's acid-base disturbance?

- A. Metabolic acidosis and metabolic alkalosis (0%)
- ✗ B. Metabolic acidosis and respiratory acidosis (1%)
- ✓ C. Metabolic acidosis and respiratory alkalosis (83%)
- D. Metabolic alkalosis and respiratory acidosis (4%)
- E. Metabolic alkalosis and respiratory alkalosis (9%)

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Correct answer
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83% Answered correctly
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Incorrect
Correct answer

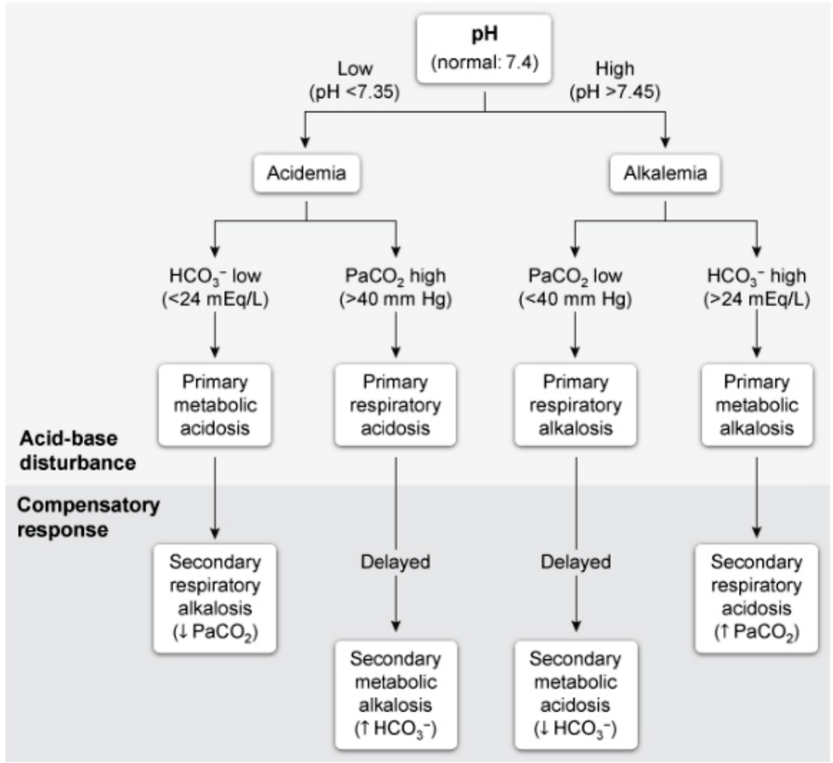
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Arterial blood gas interpretation of acid-base disorders



* The normal ranges for $PaCO_2$ and HCO_3^- vary slightly around 40 mm Hg and 24 mEq/L.
For simplicity, these numbers should be used as a normal baseline for acid-base calculations.

HCO_3^- = bicarbonate; **$PaCO_2$** = partial pressure of carbon dioxide in arterial blood.

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This patient's elevated pH and low $PaCO_2$ (<40 mm Hg) are suggestive of **primary respiratory alkalosis**. Normally, serum bicarbonate is expected to drop in response. However, a bicarbonate of 13 mEq/L is much lower than the expected secondary compensation, which indicates a second primary acid-base disorder. The lower-than-expected serum bicarbonate with a high anion gap [139 − (98 + 13) = 28] is consistent with a concomitant **primary anion gap metabolic acidosis**. This mixed respiratory alkalosis and anion gap metabolic acidosis is most likely the result of **salicylate poisoning**:

- Primary respiratory alkalosis is due to direct stimulation of the medullary respiratory center by excess salicylate, resulting in both an **increased respiratory rate** and **tidal volume** (ie, increased minute ventilation).
- Primary metabolic acidosis occurs mostly because salicylate uncouples oxidative phosphorylation, which results in **increased production of lactic acid** and ketoacids in peripheral tissues. Excess salicylic acid in the serum also makes a minor contribution. The ionized form of these compounds also increases the anion gap (unmeasured anions).

The pH is typically near or within normal range in patients with salicylate poisoning because of the opposing influences of the respiratory alkalosis and metabolic acidosis.

(Choice A) Primary metabolic acidosis and primary metabolic alkalosis can simultaneously develop in the setting of 2 disparate pathologic processes (eg, renal failure and vomiting). The pH and bicarbonate levels can be increased, normal, or decreased, depending on the severity of the metabolic acidosis compared with the metabolic alkalosis.

(Choice B) Primary metabolic acidosis with primary respiratory acidosis (eg, sepsis and hypoventilatory respiratory failure) typically leads to significant acidemia (very low pH) with low bicarbonate and high $PaCO_2$.

(Choice D) Primary metabolic alkalosis with primary respiratory acidosis (eg, vomiting and hypoventilation due to opioid overdose) is expected to show elevated bicarbonate and $PaCO_2$; the pH can reflect alkalemia or acidemia, depending on the relative severity of the 2 disturbances.

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- Primary respiratory alkalosis is due to direct stimulation of the medullary respiratory center by excess salicylate, resulting in both an **increased respiratory rate** and **tidal volume** (ie, increased minute ventilation).
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(Choice D) Primary metabolic alkalosis with primary respiratory acidosis (eg, vomiting and hypoventilation due to opioid overdose) is expected to show elevated bicarbonate and $PaCO_2$; the pH can reflect alkalemia or acidemia, depending on the relative severity of the 2 disturbances.

(Choice E) Primary metabolic alkalosis with primary respiratory alkalosis (eg, vomiting and hyperventilation due to anxiety) is expected to cause significant alkalemia (very high pH) with high bicarbonate and low $PaCO_2$.

Educational objective:
Salicylate poisoning causes mixed primary respiratory alkalosis and primary anion gap metabolic acidosis. Mixed acid-base disturbances can be recognized by inappropriate secondary compensation for one of the primary disturbances, indicating that an additional primary disturbance must be present.

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Acid-base

acidosis | acidosis | alkalosis | alkalosis

Exhibit Display

Appropriate compensatory $PaCO_2$ or HCO_3^- changes in acid-base disorders	
Metabolic acidosis (acute or chronic)	Expected $PaCO_2 = (1.5 \times HCO_3^-) + 8 \pm 2$ (Winters formula)
Metabolic alkalosis (acute or chronic)	~7 mm Hg ↑ in $PaCO_2$ per 10 mEq/L ↑ in HCO_3^-
Respiratory acidosis (chronic only*)	~4 mEq/L ↑ in HCO_3^- per 10 mm Hg ↑ in $PaCO_2$
Respiratory alkalosis (chronic only*)	~4 mEq/L ↓ in HCO_3^- per 10 mm Hg ↓ in $PaCO_2$
*Compensation for respiratory disturbances is minimal in the acute setting. The full level of chronic compensation is achieved after ~72 hr. For simplicity, normal baseline $PaCO_2$ & HCO_3^- should be considered 40 mm Hg & 24 mEq/L, respectively.	

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The pH is typically near or within normal range in patients with salicylate poisoning because of the opposing

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Acid-base

acidosis | acidosis | alkalosis | alkalosis

Exhibit Display

Anion gap metabolic acidosis	
Calculation	Anion gap = sodium – (chloride + bicarbonate) (normal: 10-14 mEq/L)
Common causes Mnemonic: MUDPILES	• Methanol • Uremia • Diabetic ketoacidosis • Propylene glycol/paraldehyde • Isoniazid/iron • Lactic acidosis • Ethylene glycol (antifreeze) • Salicylate (aspirin)

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The pH is typically near or within normal range in patients with salicylate poisoning because of the opposing

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A 32-year-old man with a history of chronic hepatitis B infection is evaluated for generalized edema. Kidney disease is suspected, and renal biopsy is performed. Histologic sections of the kidney show diffuse glomerular hypercellularity and diffuse thickening of the capillary walls. Immunofluorescence demonstrates prominent staining for IgG and C3 with coarse, granular basement membrane and mesangial positivity. Electron microscopy shows extensive subendothelial and mesangial deposits. Which of the following is the most likely diagnosis?

- A. Amyloidosis
- B. Focal segmental glomerulosclerosis
- C. Membranoproliferative glomerulonephritis
- D. Membranous nephropathy
- E. Polyarteritis nodosa

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- A. Amyloidosis (1%)
- B. Focal segmental glomerulosclerosis (6%)
- ✓ C. Membranoproliferative glomerulonephritis (65%)
- D. Membranous nephropathy (22%)
- E. Polyarteritis nodosa (4%)

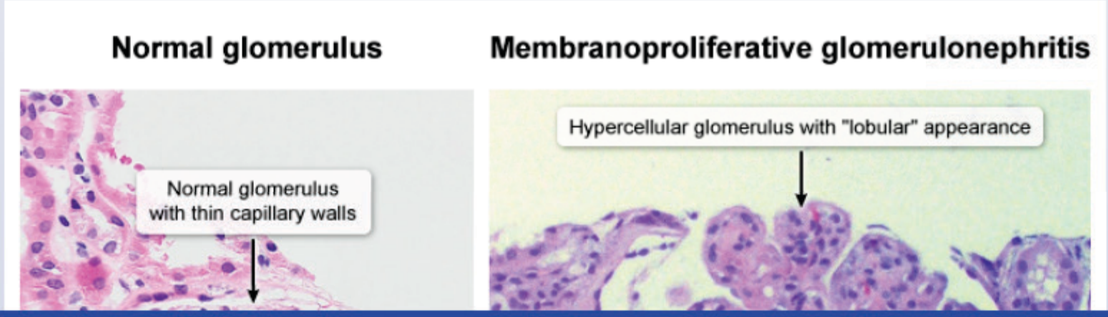
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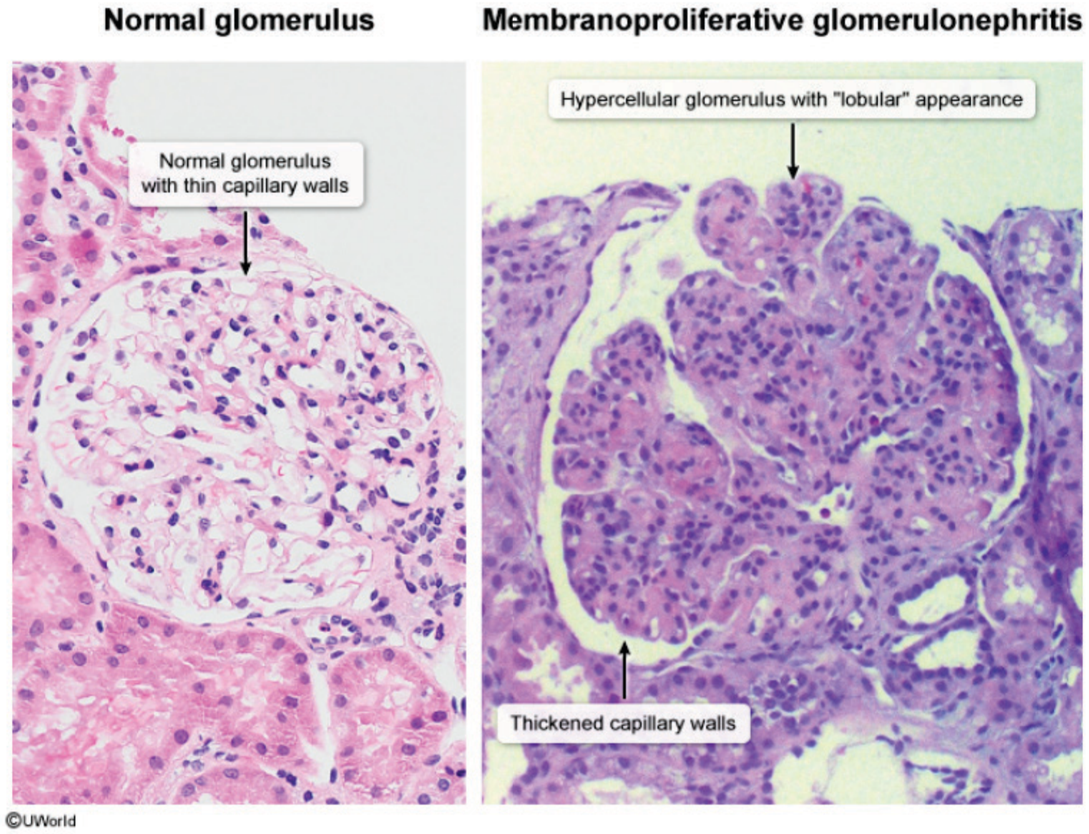
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This patient's kidney biopsy findings are consistent with **membranoproliferative glomerulonephritis** (MPGN). The most common type, MPGN type I, is caused by glomerular **immune complex deposition** in the capillary walls and mesangium. The antigen-antibody complexes typically arise from chronic infection (eg, **hepatitis B virus**, hepatitis C virus), autoimmune disease (eg, systemic lupus erythematosus), or malignancy (eg, chronic lymphocytic leukemia). In some cases, however, the underlying etiology is unknown (ie, primary MPGN).

These immune complexes activate complement pathways, resulting in inflammatory glomerular damage that can cause symptoms of nephrotic (eg, proteinuria, edema) and nephritic syndrome (eg, hematuria).

Microscopic examination shows a characteristic pattern of glomerular injury:

- Light microscopy (LM) shows large, lobular glomeruli that are **hypercellular** due to the proliferation of mesangial cells, endothelial cells, and leukocytes. Immune complex deposition results in **thickened capillary walls**, as well as the synthesis of new basement membrane material, which imparts a split (ie, **tram track**) appearance seen with special stains.
- Immunofluorescence demonstrates a **granular pattern** of IgG and C3 deposition within the capillary walls and mesangium.
- Electron microscopy (EM) shows **subendothelial** (ie, between the glomerular basement membrane and endothelium) and **mesangial deposits**.

(Choice A) Amyloidosis commonly involves the kidney and can cause nephrotic syndrome. However, LM demonstrates amorphous, eosinophilic glomerular deposits (composed of misfolded proteins) that show apple-green birefringence under polarized light when stained with Congo red.

(Choice B) Focal segmental glomerulosclerosis also causes nephrotic syndrome, but LM shows sclerosis that affects portions of some glomeruli. It is more often associated with HIV infection than hepatitis B infection.

(Choice D) Membranous nephropathy is a common cause of nephrotic syndrome that may be associated with

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mesangial cells, endothelial cells, and leukocytes. Immune complex deposition results in **thickened capillary walls**, as well as the synthesis of new basement membrane material, which imparts a split (ie, **tram track**) appearance seen with special stains.

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- Electron microscopy (EM) shows **subendothelial** (ie, between the glomerular basement membrane and endothelium) and **mesangial deposits**.

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(Choice B) Focal segmental glomerulosclerosis also causes nephrotic syndrome, but LM shows sclerosis that affects portions of some glomeruli. It is more often associated with HIV infection than hepatitis B infection.

(Choice D) Membranous nephropathy is a common cause of nephrotic syndrome that may be associated with hepatitis B infection. However, LM shows diffuse thickening of the glomerular capillary walls without significant hypercellularity. EM demonstrates subepithelial (not subendothelial) deposits.

(Choice E) Polyarteritis nodosa is a systemic vasculitis that often affects medium-sized arteries in the kidney. It is associated with chronic hepatitis B infection, but LM shows transmural arterial inflammation with fibrinoid necrosis (eg, fibrin deposition in the vessel wall).

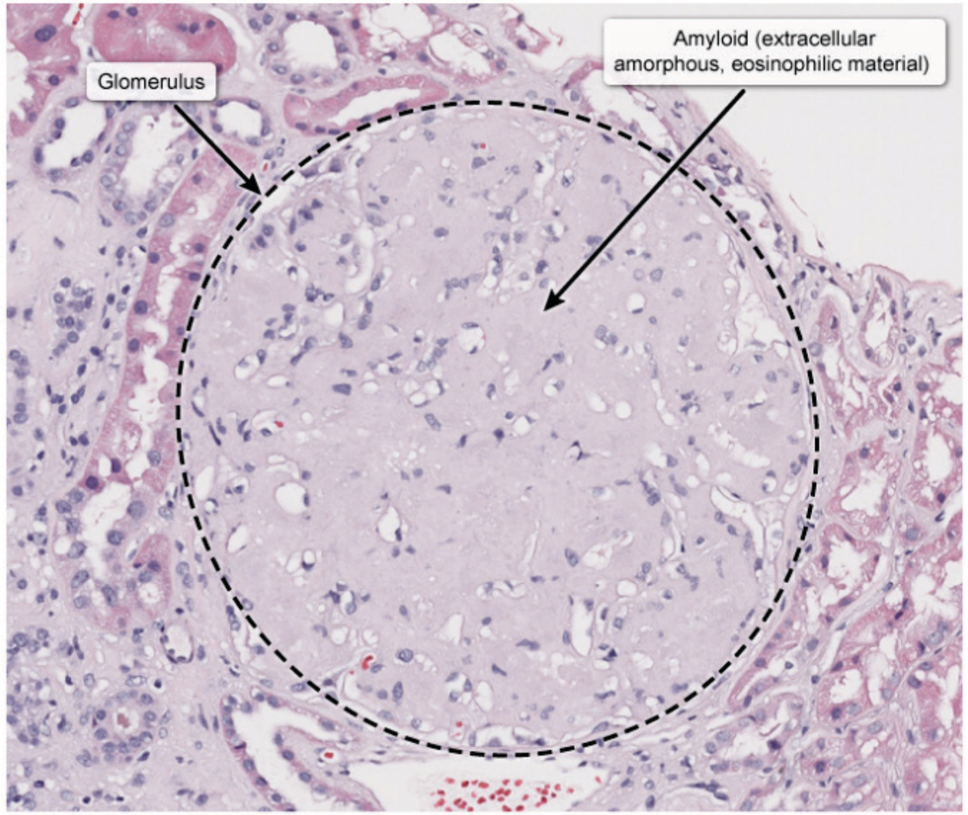
Educational objective:
Membranoproliferative glomerulonephritis is typically caused by immune complex deposition within the glomerular capillary walls and mesangium and can be associated with chronic infections (eg, hepatitis B). It is characterized by large, hypercellular glomeruli with thickened capillary walls. Immunofluorescence typically shows a granular pattern of IgG and C3. Electron microscopy shows subendothelial and mesangial deposits.

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Microscopic examination shows a characteristic pattern of glomerular injury:

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Renal amyloidosis



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Membranoproliferative glomerulonephritis is typically caused by immune complex deposition within the glomerular capillary walls and mesangium and can be associated with chronic infections (eg, hepatitis B). It is characterized

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Microscopic examination shows a characteristic pattern of glomerular injury:

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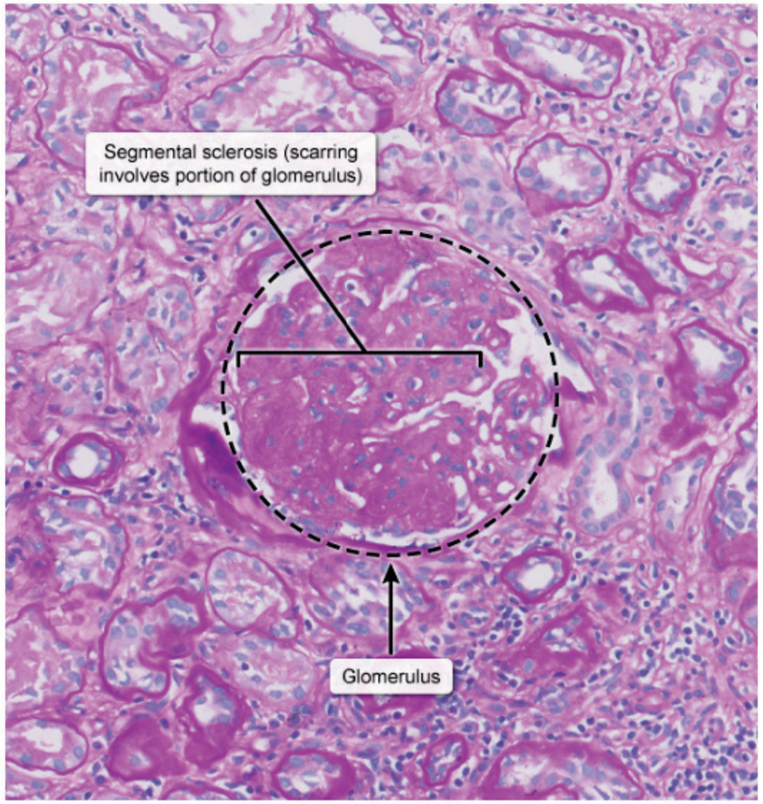
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Membranoproliferative glomerulonephritis is typically caused by immune complex deposition within the glomerular capillary walls and mesangium and can be associated with chronic infections (eg, hepatitis B). It is characterized

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Focal segmental glomerulosclerosis



Periodic acid–Schiff (PAS) stain

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A 48-year-old woman comes to the emergency department due to worsening headache, blurred vision, and nausea for the past several days. She also has had decreased urine output. Medical history is significant for systemic sclerosis. Blood pressure is 190/110 mm Hg and pulse is 96/min. Physical examination shows diffuse skin thickening involving the hands, face, and anterior chest. There are no focal neurologic deficits, but a flame-shaped retinal hemorrhage is present. Laboratory studies reveal elevated serum blood urea nitrogen and creatinine levels, which were within normal limits during a recent office visit. Urine microscopy shows no sediment. A primary injury to which of the following structures is the most likely cause of this patient's acute kidney injury?

- A. Large systemic vessels
- B. Postrenal urinary tract
- C. Renal glomeruli
- D. Renal interstitium
- E. Renal tubules
- F. Small renal vessels

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- A. Large systemic vessels (15%)
- ✗ B. Postrenal urinary tract (2%)
- C. Renal glomeruli (20%)
- D. Renal interstitium (9%)
- E. Renal tubules (9%)
- ✓ F. Small renal vessels (42%)

Incorrect
Correct answer
F

42%
Answered correctly

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Explanation

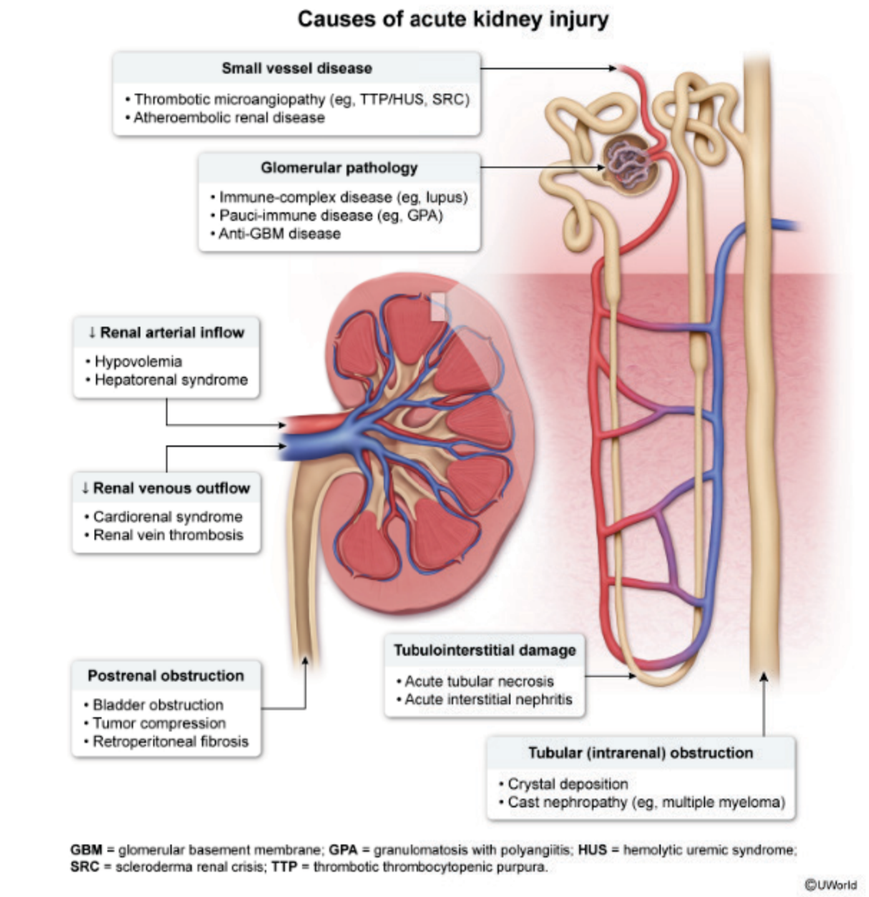
Causes of acute kidney injury

Small vessel disease
• Thrombotic microangiopathy (eg, TTP/HUS, SRC)

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✓ ○ F. Small renal vessels (42%)

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Systemic sclerosis (SS) (ie, scleroderma) is an autoimmune disease that damages connective tissue and small blood vessels throughout the body. This patient's **acute renal failure** and **severe hypertension** (eg, retinal hemorrhage, headache) are consistent with a life-threatening complication of SS known as **scleroderma renal crisis** (SRC). SRC is caused by immune-mediated injury to **small renal vessels** that typically spares the glomerular capillaries; therefore, dysmorphic red blood cells (RBCs) and RBC casts are *not* present on urine microscopy, unlike in patients with glomerulonephritis **(Choice C)**. Vascular changes in SRC include:

- Intimal thickening and proliferation of endothelial and smooth muscle cells
- Vasospasm and vascular occlusions
- Fibrinoid necrosis involving the entire blood vessel

Histopathologic changes in SRC are similar to malignant nephrosclerosis caused by severe primary hypertension. Patients with severe primary hypertension develop these changes as a direct result of vascular barotrauma. In contrast, patients with SRC develop hypertension due to vascular narrowing and obliteration, which results in **renal hypoperfusion**. Renal hypoperfusion leads to renal failure and activation of the **renin-angiotensin-aldosterone system** (RAAS), which promotes systemic vasoconstriction, thereby resulting in severe hypertension. Therefore, first-line treatment for SRC is RAAS blockade with an ACE inhibitor, even in the presence of renal failure.

(Choice A) Vasculitis of large systemic vessels is a characteristic finding in Takayasu arteritis, which can lead to renovascular hypertension via inflammation-induced narrowing of the large renal artery. However, acute renal failure has only rarely been described in patients with Takayasu arteritis, likely because bilateral renal artery involvement would be necessary in most patients.

(Choice B) Obstruction of the postrenal urinary tract (eg, bilateral ureteral compression, bladder outlet obstruction) can lead to renal failure, but this patient's skin changes and severe hypertension make SRC more likely.

(Choices D and E) Tubulointerstitial diseases (eg, interstitial nephritis) typically cause an active urine sediment (eg, white blood cell casts). Tubulointerstitial involvement is sometimes seen with certain autoimmune diseases

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- Vasospasm and vascular occlusions
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(Choices D and E) Tubulointerstitial diseases (eg, interstitial nephritis) typically cause an active urine sediment (eg, white blood cell casts). Tubulointerstitial involvement is sometimes seen with certain autoimmune diseases (eg, sarcoidosis, Sjögren syndrome), but it is not typical of SS.

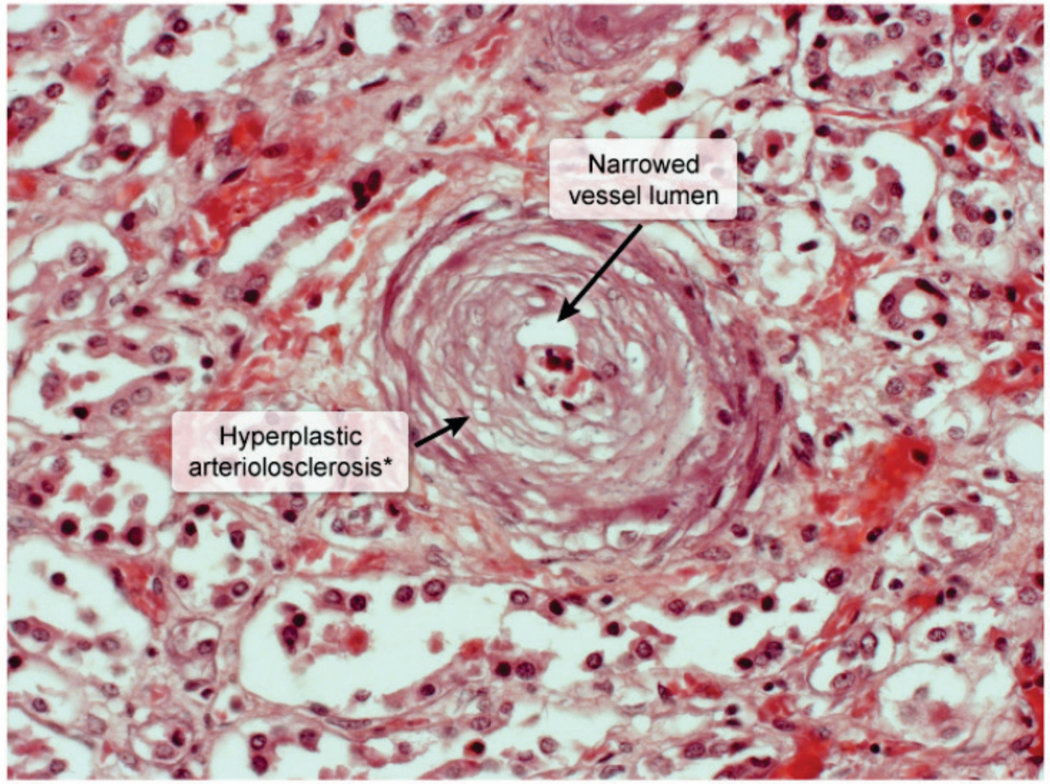
Educational objective:
Scleroderma renal crisis (SRC) is a life-threatening complication of systemic sclerosis characterized by acute renal failure and severe hypertension. SRC is caused by immune-mediated injury to small renal vessels that leads to reduced renal perfusion due to vascular narrowing and obliteration.

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• Cast nephropathy (eg, multiple myeloma)

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Malignant nephrosclerosis



*Vessel wall thickened by concentric layers of collagen and smooth muscle ("onion-skinning")

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obstruction) can lead to renal failure, but this patient's skin changes and severe hypertension make SRC more

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A 64-year-old man comes to the office due to persistent back pain, constipation, and easy fatigability for the last several months. Blood pressure is 115/75 mm Hg and pulse is 88/min. The patient has dry mucous membranes. Laboratory results are as follows:

Hemoglobin	8.6 g/dL
Mean corpuscular volume	92 fL
Blood urea nitrogen	68 mg/dL
Creatinine	3.8 mg/dL
Total protein	8.9 g/dL
Albumin	3.5 g/dL

Renal biopsy is performed and light microscopy shows atrophic tubules, many of which contain large, obstructing, waxy casts that stain intensely with eosin. Which of the following is the most likely diagnosis in this patient?

- A. Acute pyelonephritis
- B. Aminoglycoside toxicity
- C. Hypersensitivity interstitial nephritis
- D. Ischemic tubular necrosis
- E. Lead nephropathy
- F. Multiple myeloma
- G. Nonsteroidal anti-inflammatory drug–associated nephropathy
- H. Papillary necrosis

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- D. Ischemic tubular necrosis
- E. Lead nephropathy
- F. Multiple myeloma
- G. Nonsteroidal anti-inflammatory drug–associated nephropathy
- H. Papillary necrosis
- I. Urate nephropathy

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Blood urea nitrogen	68 mg/dL
Creatinine	3.8 mg/dL
Total protein	8.9 g/dL
Albumin	3.5 g/dL

Renal biopsy is performed and light microscopy shows atrophic tubules, many of which contain large, obstructing, waxy casts that stain intensely with eosin. Which of the following is the most likely diagnosis in this patient?

- A. Acute pyelonephritis (2%)
- B. Aminoglycoside toxicity (1%)
- C. Hypersensitivity interstitial nephritis (6%)
- D. Ischemic tubular necrosis (18%)
- ✗ E. Lead nephropathy (2%)
- ✓ F. Multiple myeloma (53%)
- G. Nonsteroidal anti-inflammatory drug–associated nephropathy (10%)
- H. Papillary necrosis (5%)
- I. Urate nephropathy (1%)

Incorrect

53% 06 secs 2023

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Multiple myeloma	
Pathophysiology	• Plasma cell neoplasm produces **monoclonal** paraprotein (immunoglobulin)
Manifestations	• Bone pain, fractures • Constitutional symptoms (weight loss, fatigue) • Recurrent infections
Laboratory	• Normocytic anemia • Renal insufficiency • Hypercalcemia (constipation, muscle weakness) • Monoclonal paraproteinemia **(M-spike)**
Radiology	• **Osteolytic lesions**/osteopenia (osteoclast activation)

This patient with back pain, fatigue, normocytic anemia, renal failure, and a gamma gap (serum total protein minus serum albumin ≥4 g/dL) likely has **multiple myeloma** (MM). MM is a lymphoproliferative disorder characterized by monoclonal plasma cell proliferation and production of monoclonal immunoglobulins. It should be suspected in elderly patients with any combination of **hypercalcemia** (causes constipation), **normocytic anemia** (causes fatigue), **bone pain** (often in the back and ribs due to lytic lesions), elevated **gamma gap** (due to the presence of large amounts of monoclonal proteins), or **renal failure**.

Renal failure in MM is often caused by **light chain cast nephropathy**. Free light chains (Bence Jones proteins) are filtered by the glomerulus in small amounts and then reabsorbed in the tubules. When levels exceed reabsorptive capacity, light chains precipitate with Tamm-Horsfall protein and form casts that cause tubular obstruction and epithelial injury, leading to impaired renal function. On light microscopy, numerous large, glassy **eosinophilic casts** are seen. Deposition of light chain fragments in the glomerular mesangium and capillary loops can also cause renal failure in MM (amyloid light-chain amyloidosis).

(Choice A) Acute pyelonephritis presents acutely with fever, flank pain, and pyuria. White blood cell casts may be

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(Choice A) Acute pyelonephritis presents acutely with fever, flank pain, and pyuria. White blood cell casts may be present.

(Choices B and D) Both nephrotoxins (eg, aminoglycosides) and ischemia cause acute tubular necrosis, which classically presents with muddy brown, granular epithelial cell casts and tubular epithelial cells in the urine.

(Choice C) Hypersensitivity interstitial nephritis is often associated with initiation of a new medication. Eosinophilia and eosinophiluria with white cell casts containing eosinophils may be seen; however, waxy eosinophilic casts are not present.

(Choice E) Chronic lead intoxication produces chronic tubulointerstitial nephritis (interstitial fibrosis and tubular atrophy seen on light microscopy); casts are unexpected.

(Choices G and H) Nonsteroidal anti-inflammatory drugs (NSAIDs) may cause chronic interstitial nephritis or acute papillary necrosis; urinalysis may show clear, hyaline casts. Excessive NSAID use is often associated with a microcytic (from gastrointestinal bleeding) rather than normocytic anemia, and a gamma gap would not be

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(Choice I) Chronic hyperuricemia leads to urate nephropathy due to precipitation of urate crystals. On light microscopy, needle-shaped crystals are seen in the interstitium and tubular lumen.

Educational objective:
Multiple myeloma should be suspected in elderly patients with any combination of hypercalcemia, normocytic anemia, bone pain, elevated gamma gap, or renal failure. Renal failure is commonly caused by light chain cast nephropathy; large, waxy, eosinophilic casts composed of Bence Jones proteins are seen in the tubular lumen.

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A 65-year-old woman is brought to the emergency department by her family due to worsening generalized weakness and lethargy. She has had no fever, chills, vomiting, or diarrhea but has been urinating frequently over the past several days. Her family also notes that the patient has lost 5 kg (11 lb) over the past month. She takes no medications and has smoked 1-2 packs of cigarettes daily for the last 40 years. On physical examination, the patient appears ill with dry mucous membranes. There are no abnormal lung sounds or heart murmurs. The abdomen is soft and nontender. Laboratory testing shows serum calcium of 14.0 mg/dL and normal serum glucose and urinalysis. Imaging studies reveal an 8-cm right lung mass with enlarged mediastinal lymph nodes but no focal bony lesions. Serum levels of which of the following substances are most likely to be elevated in this patient?

- A. 1,25-dihydroxyvitamin D
- B. ACTH
- C. Parathyroid hormone (PTH)
- D. Phosphorus
- E. PTH-related protein
- F. Thyroxine (T4)

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- A. 1,25-dihydroxyvitamin D (5%)
- ✕ B. ACTH (4%)
- C. Parathyroid hormone (PTH) (10%)
- D. Phosphorus (1%)
- ✓ E. PTH-related protein (78%)
- F. Thyroxine (T4) (0%)

Incorrect
Correct answer
E

78%
Answered correctly

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Explanation

Hypercalcemia of malignancy			

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Hypercalcemia of malignancy			
Cause	**Tumor type**	**Mechanism**	**Diagnostic**
PTHrP*	• Squamous cell • Kidney & bladder • Breast & ovarian	• PTH mimic	• ↓ PTH • ↑ PTHrP
Bone metastases	• Breast • Multiple myeloma	• ↑ Osteolysis	• ↓ PTH & PTHrP • ↓ Vitamin D
1,25-dihydroxyvitamin D	• Lymphoma	• ↑ Calcium absorption	• ↓ PTH • ↑ Vitamin D
*PTHrP causes ~80% of malignancy-associated hypercalcemia. **PTH** = parathyroid hormone; **PTHrP** = PTH-related protein.			

This patient has **symptomatic hypercalcemia**, which typically occurs in patients with a serum calcium of >12 mg/dL and manifests with weakness, neuropsychiatric symptoms (eg, lethargy), gastrointestinal symptoms (eg, constipation, nausea), or kidney stones. Severe hypercalcemia results in impairment of the concentrating capacity of the distal tubule, leading to polyuria and volume depletion. Mild hypercalcemia is usually due to benign causes (eg, primary hyperparathyroidism), but serum calcium >13 mg/dL suggests an underlying malignancy.

Humoral hypercalcemia of malignancy (HHM) is the most common cause of hypercalcemia in patients with malignancy and is due to secretion of **parathyroid hormone-related peptide** (PTHrP) by malignant cells. PTHrP closely resembles PTH at the bioactive amino-terminal region and causes increased bone resorption, decreased renal excretion of calcium, and increased renal excretion of phosphorus (leading to hypophosphatemia **[Choice D]**). However, unlike PTH, PTHrP does not significantly increase 1,25-dihydroxyvitamin D production due to structural differences after the first 13 amino acids.

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HHM occurs most commonly in squamous cell (ie, lung, head and neck), renal, bladder, breast, and ovarian carcinomas. This patient's heavy smoking history, weight loss, and lung mass suggest squamous cell carcinoma of the lung. Hypercalcemia can also occur due to osteolytic bony metastasis (eg, breast cancer, multiple myeloma), but this is less common than HHM and this patient has no lytic lesions visible on imaging.

(Choice A) Hodgkin lymphoma and granulomatous diseases (eg, sarcoidosis) can express 1-alpha-hydroxylase, which increases the formation of 1,25-dihydroxyvitamin D, leading to hypercalcemia. However, this patient's large lung mass with regional lymph node enlargement is more suggestive of primary squamous cell carcinoma of the lung.

(Choice B) Ectopic ACTH secretion causes paraneoplastic Cushing syndrome, characterized by hypertension, hyperpigmentation, and proximal muscle weakness. Laboratory studies typically show hyperglycemia rather than hypercalcemia.

(Choice C) Ectopic production of PTH is a very rare cause of hypercalcemia in patients with malignancy. Patients with HHM have very low levels of PTH due to feedback suppression by hypercalcemia.

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(Choice C) Ectopic production of PTH is a very rare cause of hypercalcemia in patients with malignancy. Patients with HHM have very low levels of PTH due to feedback suppression by hypercalcemia.

(Choice F) Thyrotoxicosis can cause mild hypercalcemia due to increased bone turnover, but severe hypercalcemia is rare, and this patient's high calcium level and lung mass is more suggestive of an underlying malignancy.

Educational objective:
Serum calcium >13 mg/dL is suggestive of an underlying malignancy. Secretion of parathyroid hormone-related protein (PTHrP), which closely resembles parathyroid hormone at the bioactive amino-terminal region, is a frequent cause of malignancy-related hypercalcemia and is commonly seen with squamous cell carcinomas (eg, lung, neck).

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A 30-year-old woman is evaluated for almost daily headaches and intermittent blurry vision. Medical history includes obesity but no other chronic conditions. Physical examination shows bilateral symmetric papilledema. There are no other focal neurological deficits. Brain imaging is normal, and blood cell counts and serum chemistry studies are within normal limits. Lumbar puncture reveals an elevated opening pressure, and idiopathic intracranial hypertension is diagnosed. Weight loss is advised, and the patient is prescribed acetazolamide therapy. Which of the following changes are most likely to occur in this patient over the next several days due to the medication?

	$PaCO_2$	Total serum calcium	Urine potassium	Urine pH
○ A.	Decrease	Decrease	Increase	Decrease
○ B.	Decrease	Decrease	Increase	Increase
○ C.	Decrease	No change	Decrease	Increase
○ D.	Increase	Decrease	Increase	Decrease
○ E.	Increase	Increase	Increase	Decrease

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	$PaCO_2$	Total serum calcium	Urine potassium	Urine pH	
✗ A.	Decrease	Decrease	Increase	Decrease	(15%)
✓ B.	Decrease	Decrease	Increase	Increase	(39%)
C.	Decrease	No change	Decrease	Increase	(27%)
D.	Increase	Decrease	Increase	Decrease	(12%)
E.	Increase	Increase	Increase	Decrease	(4%)

Incorrect
Correct answer
B

39%
Answered correctly

03 secs
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Explanation

Diuretic effects on total body electrolyte levels

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Diuretic effects on total body electrolyte levels					
Diuretic type	**Na^+**	**K^+**	**HCO_3^-**	**Ca^{2+}**	**Uric acid**
Loop (eg, furosemide)	↓↓↓	↓↓	↑↑	↓	↑
Thiazide (eg, HCTZ, metolazone)	↓↓	↓	↑	↑	↑
Potassium sparing (eg, spironolactone, amiloride)	↓	↑	↓	—	—
Carbonic anhydrase inhibitor (eg, acetazolamide)	↓	↓	↓	↓	—
HCTZ = hydrochlorothiazide.					

Acetazolamide is a **carbonic anhydrase inhibitor** that acts as a weak diuretic. The drug also reduces intracranial pressure and improves symptoms in patients with **idiopathic intracranial hypertension**. This effect occurs independent of the kidneys and likely results from a decreased rate of cerebrospinal fluid production by the choroid plexus.

Carbonic anhydrase inhibitors block reabsorption of sodium bicarbonate ($NaHCO_3$) in the proximal tubule, leading to increased **excretion of HCO_3^-**. This **alkalinizes the urine** (increased pH) **(Choice A)** while reducing blood pH to cause a mild metabolic acidosis. In response, ventilation is increased to facilitate CO_2 removal and **decrease blood $PaCO_2$** (compensatory respiratory alkalosis).

The overall diuretic effect is weak because most of the Na^+ blocked from reabsorption in the proximal tubule is

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The overall diuretic effect is weak because most of the Na^+ blocked from reabsorption in the proximal tubule is reabsorbed more distally. Increased distal reabsorption of Na^+ stimulates increased K^+ excretion, leading to **increased urine potassium** and mild hypokalemia. Because paracellular calcium (Ca^{2+}) reabsorption is coupled to Na^+ reabsorption in the proximal tubule, urinary Ca^{2+} excretion is slightly increased (total serum Ca^{2+} is slightly reduced).

(Choice C) Potassium-sparing diuretics (eg, spironolactone) block Na^+ reabsorption in the collecting duct while increasing the reabsorption of K^+ and H^+. This decreases urine potassium and increases urine pH. Mild metabolic acidosis is generated with compensatory respiratory alkalosis. Ca^{2+} and other electrolytes are not significantly affected.

(Choice D) Loop diuretics (eg, furosemide) block the $Na^+K^+2Cl^-$ transporter in the ascending loop of Henle. This causes potent excretion of Na^+, K^+, and Cl^- (increased urine potassium) and impairs passive Ca^{2+} reabsorption, decreasing serum calcium. There is also aldosterone-mediated H^+ loss, and the Cl^- depletion impairs HCO_3^- excretion, leading to decreased urine pH and metabolic alkalosis with compensatory respiratory acidosis (increased $PaCO_2$).

(Choice E) Thiazide diuretics (eg, hydrochlorothiazide) block the Na^+Cl^- transporter in the distal convoluted

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blood $PaCO_2$ (compensatory respiratory alkalosis).

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(Choice E) Thiazide diuretics (eg, hydrochlorothiazide) block the Na^+Cl^- transporter in the distal convoluted tubule. Ca^{2+} reabsorption is increased, leading to increased serum calcium. Otherwise, the effects are the same as those with loop diuretics but with less potency.

Educational objective:
Carbonic anhydrase inhibitors (eg, acetazolamide) are weak diuretics that block reabsorption of sodium bicarbonate ($NaHCO_3$) in the proximal tubule. The main effect is increased HCO_3^- excretion, leading to increased urine pH, mild metabolic acidosis (with compensatory respiratory alkalosis), mild hypokalemia, and mild hypocalcemia.

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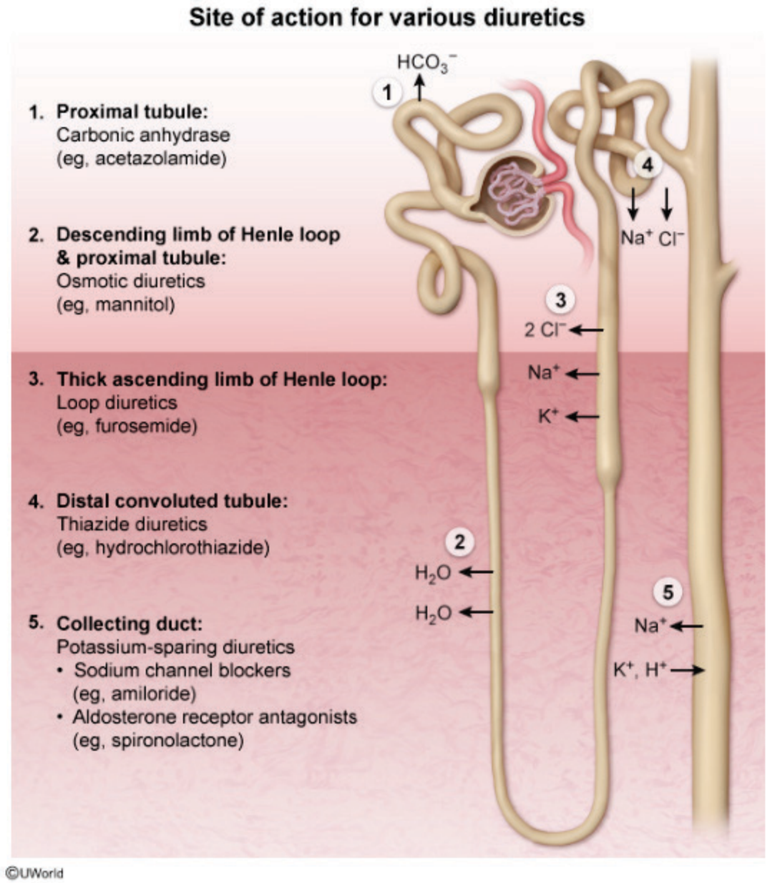
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as those with loop diuretics but with less potency.

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independent of the kidneys and likely results from a decreased rate of cerebrospinal fluid production by the choroid plex

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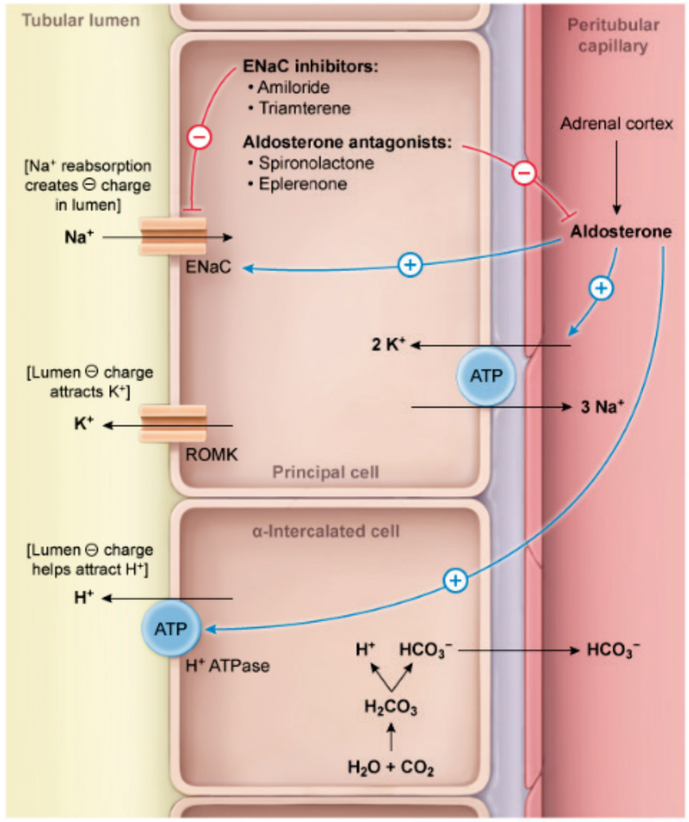
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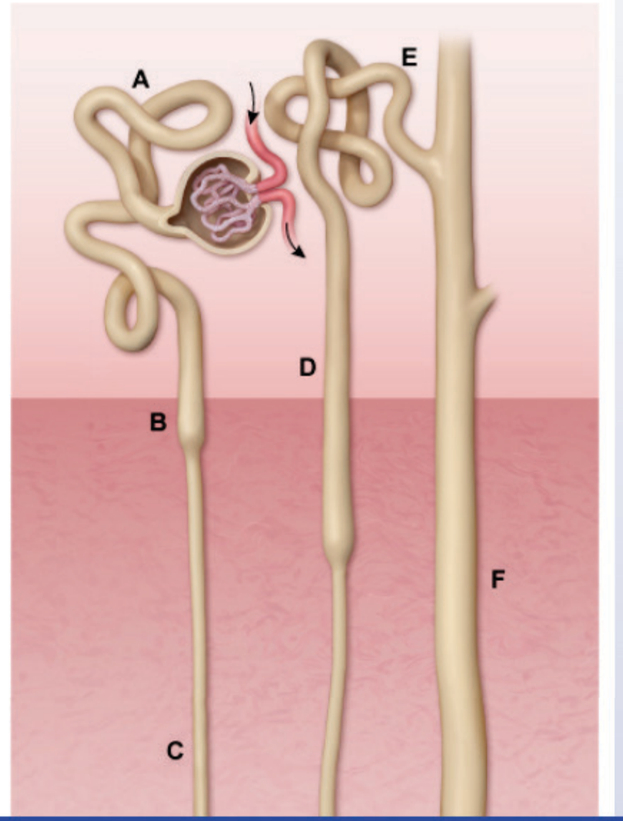
Action of aldosterone in the collecting duct of the nephron



ENaC = epithelial sodium channel; **ROMK** = renal outer medullary potassium channel. ©UWorld

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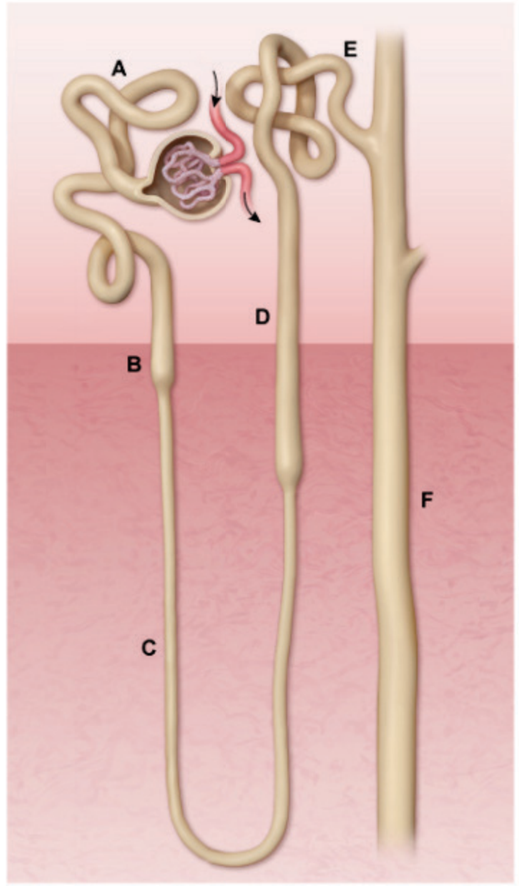
A 34-year-old woman comes to the physician complaining of frequent urination. She has tried limiting her fluid intake but found it difficult because she got very thirsty. The physician assesses the water-conserving function of her kidneys by performing a water restriction test, which shows inappropriately dilute urine. Laboratory studies drawn during the period of water deprivation show low vasopressin levels. The physician diagnoses the patient with central diabetes insipidus and explains that her kidneys are unable to absorb the proper amount of water due to defective hormone production. Which of the following areas of the nephron is normally impermeable to water regardless of serum vasopressin levels?



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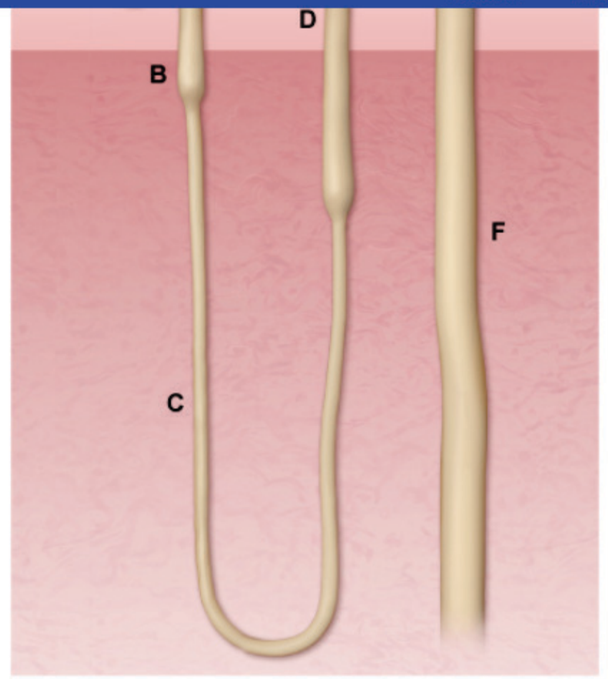
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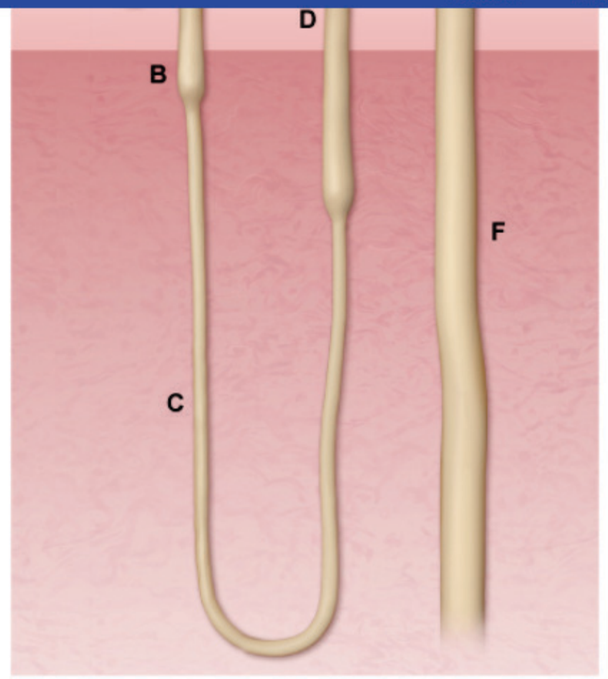
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- A. A
- B. B
- C. C
- D. D
- E. E
- F. F

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- A. A (1%)
- ✕ B. B (1%)
- C. C (15%)
- ✓ D. D (73%)
- E. E (4%)
- F. F (3%)

Incorrect
Correct answer
D

73%
Answered correctly

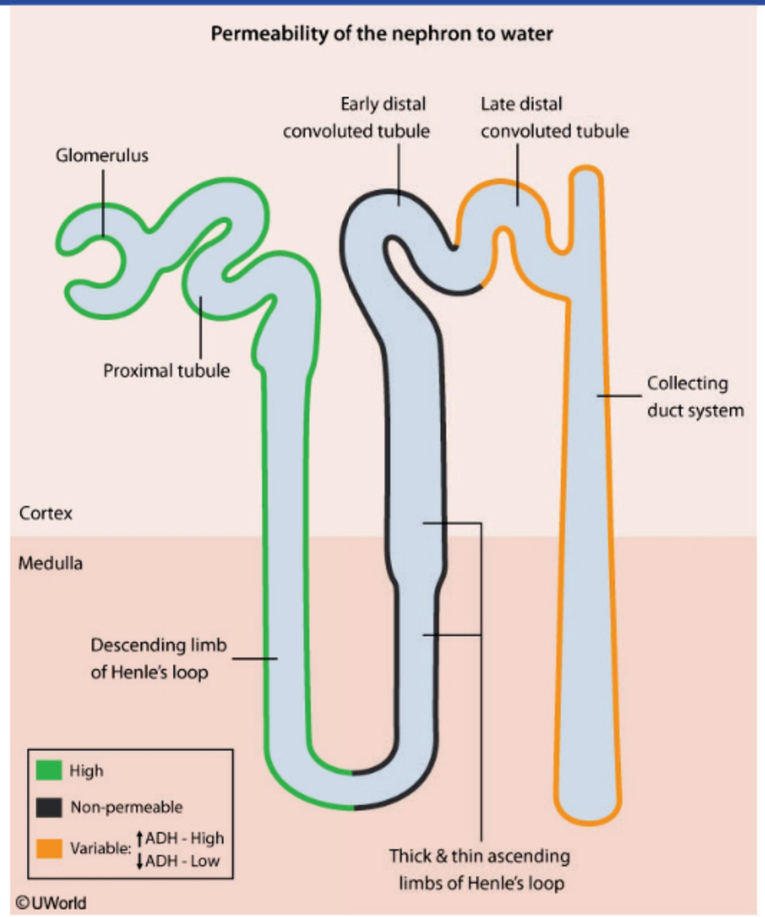
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F. F (3%)

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Free water excretion by the kidney depends primarily on serum vasopressin (antidiuretic hormone) levels. This hormone acts on the nephron to regulate the osmotic pressure of body fluids by varying the water permeability of the distal portion of the nephron. Water and electrolyte permeability varies in different regions of the nephron as follows:

1. Glomerular capillaries are fenestrated and therefore highly permeable to water and other solutes. The glomeruli collectively filter about 180 L of isotonic fluid (equal to plasma osmolarity) into Bowman's space daily.
2. The proximal convoluted tubule actively reabsorbs electrolytes, glucose, and amino acids. Water reabsorption in the proximal tubule occurs passively along with transport of solutes into the epithelial cells; thus, tubular fluid remains isotonic.
3. The loop of Henle is located in the renal medulla, where the interstitium is hypertonic (higher osmolarity than that of plasma). The descending limb of the loop of Henle is permeable to water, but most of the ions are retained in the lumen **(Choice C)**. As water moves into the interstitium, the fluid left in the lumen becomes hypertonic.
4. The thick and thin ascending limbs of the loop of Henle are impermeable to water. In the ascending limb, the osmolarity of the tubular fluid decreases due to passive adsorption of NaCl in the thin region as well as active transport of electrolytes out of the lumen by the $Na^+/K^+/2Cl^-$ cotransporter in the thick portion.
5. Water permeability of the early distal convoluted tubule is also very low, and more electrolytes than water are reabsorbed. However, water permeability in the late distal tubule can vary based on vasopressin levels **(Choice E)**. Urinary pH is regulated chiefly through H^+ secretion by intercalated cells in the late distal and collecting tubules.
6. The water permeability of the cortical and medullary collecting ducts is also regulated by vasopressin **(Choice F)**. If the water intake of the individual is high, vasopressin is not released and water permeability of the collecting duct system is low, producing dilute urine. In contrast, water deprivation stimulates vasopressin secretion, leading to marked reabsorption of water in the collecting ducts and the production of low-volume,

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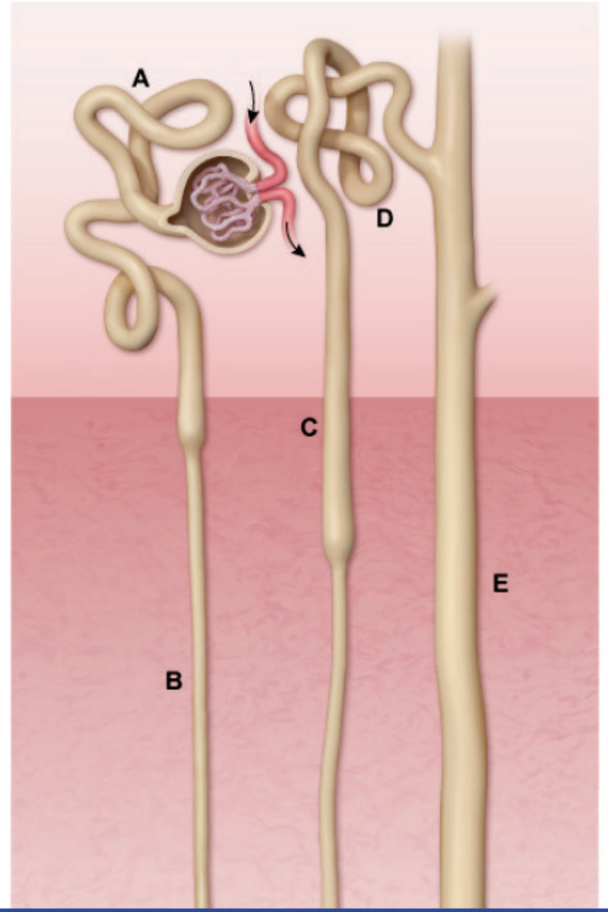
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6. The water permeability of the cortical and medullary collecting ducts is also regulated by vasopressin **(Choice F)**. If the water intake of the individual is high, vasopressin is not released and water permeability of the collecting duct system is low, producing dilute urine. In contrast, water deprivation stimulates vasopressin secretion, leading to marked reabsorption of water in the collecting ducts and the production of low-volume, high-osmolar urine.

Educational objective:

The ascending limb of the loop of Henle is impermeable to water regardless of serum vasopressin levels. Reabsorption of electrolytes by the $Na^+/K^+/2Cl^-$ cotransporter occurs in the thick ascending limb and contributes to formation of the corticomedullary concentration gradient.

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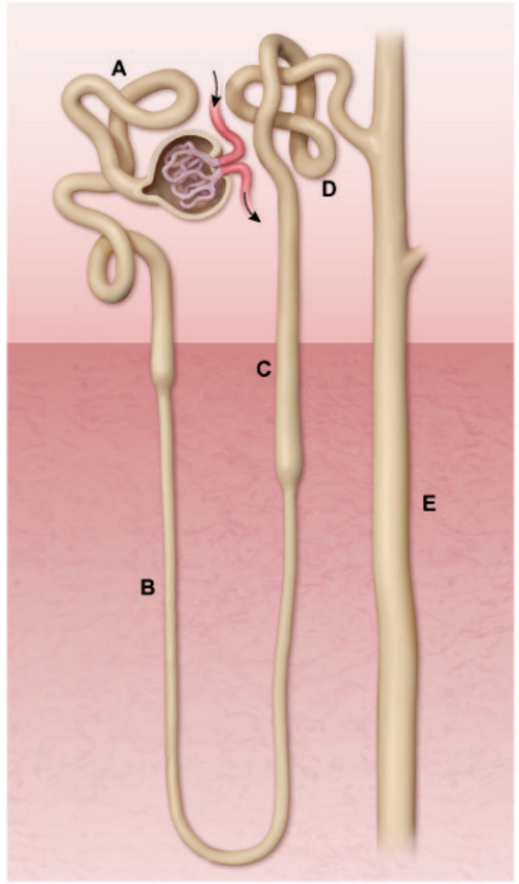
A 57-year-old man comes to the emergency department due to the abrupt onset of severe right eye pain and ipsilateral headache. The patient also has severe nausea and describes seeing halos around objects. After initial treatment with the appropriate medication, the pain severity decreases. Urine output also slightly increases, and the urine pH becomes more alkaline. The medication used to treat this patient's eye condition predominantly acts on which of the following nephron segments?



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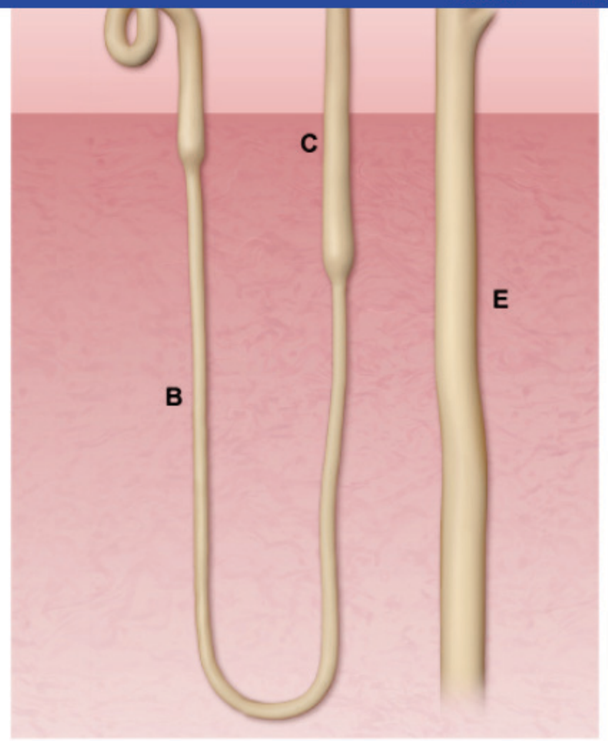
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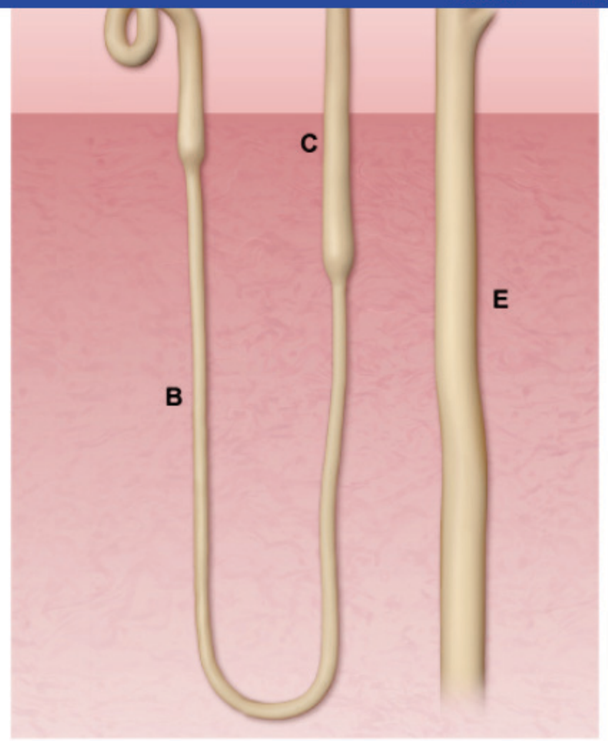
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- A. A
- B. B
- C. C
- D. D
- E. E

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- ✓ A. A (72%)
- ✗ B. B (5%)
- C. C (4%)
- D. D (6%)
- E. E (10%)

Incorrect
Correct answer
A

72%
Answered correctly

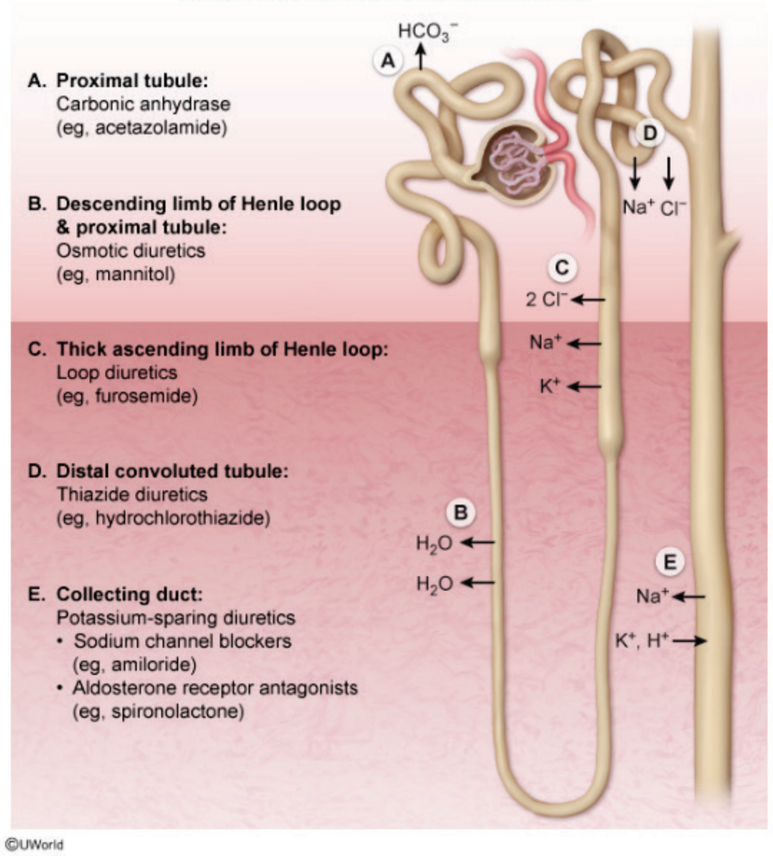
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aqueous humor. Aqueous humor production is promoted by **carbonic anhydrase**; carbonic anhydrase inhibitors

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This patient with abrupt-onset unilateral headache and eye pain with nausea and visual halos likely has acute **angle-closure glaucoma**, which characterized by increased intraocular pressure caused by impaired drainage of aqueous humor. Aqueous humor production is promoted by **carbonic anhydrase**; carbonic anhydrase inhibitors (eg, **acetazolamide**) rapidly reduce intraocular pressure in patients with glaucoma.

Carbonic anhydrase is also present in the **renal proximal tubules**, where it catalyzes reactions necessary for bicarbonate (HCO_3) reabsorption. By inhibiting carbonic anhydrase, acetazolamide blocks reabsorption of HCO_3^- in the proximal tubule; the resulting urinary loss of HCO_3^- leads to mild diuresis with increased urine pH and consequent mild **metabolic acidosis**. Acetazolamide is often used to help offset the metabolic alkalosis that is commonly caused by loop diuretics.

(Choice B) The descending limb of the loop of Henle is very permeable to water, allowing passive water diffusion to produce more concentrated urine. Osmotic diuretics (eg, mannitol) reduce water reabsorption in this region. Although mannitol can reduce intraocular pressure, it does not increase urine pH (mannitol may slightly acidify the urine due to reduced reabsorption of H^+).

(Choice C) Loop diuretics (eg, furosemide) are the mainstay of diuretic therapy for heart failure because they inhibit the Na^+-K^+-$2Cl^-$ cotransporter in the thick ascending loop to stimulate potent excretion of Na^+ and water, thereby reducing total body fluid volume.

(Choice D) Thiazide diuretics (eg, metolazone) act distally in the nephron and potentiate the diuretic effect of loop diuretics by blocking the reabsorption of increased Na^+ delivered to the distal convoluted tubules, producing a profound synergistic diuresis.

(Choice E) Potassium-sparing diuretics (eg, spironolactone, amiloride) act on the collecting tubules and ducts, where they have a mild diuretic effect by inhibiting reabsorption of the remaining Na^+ in the nephron. They are often used to offset hypokalemia from more potent diuretics by reducing K^+ secretion.

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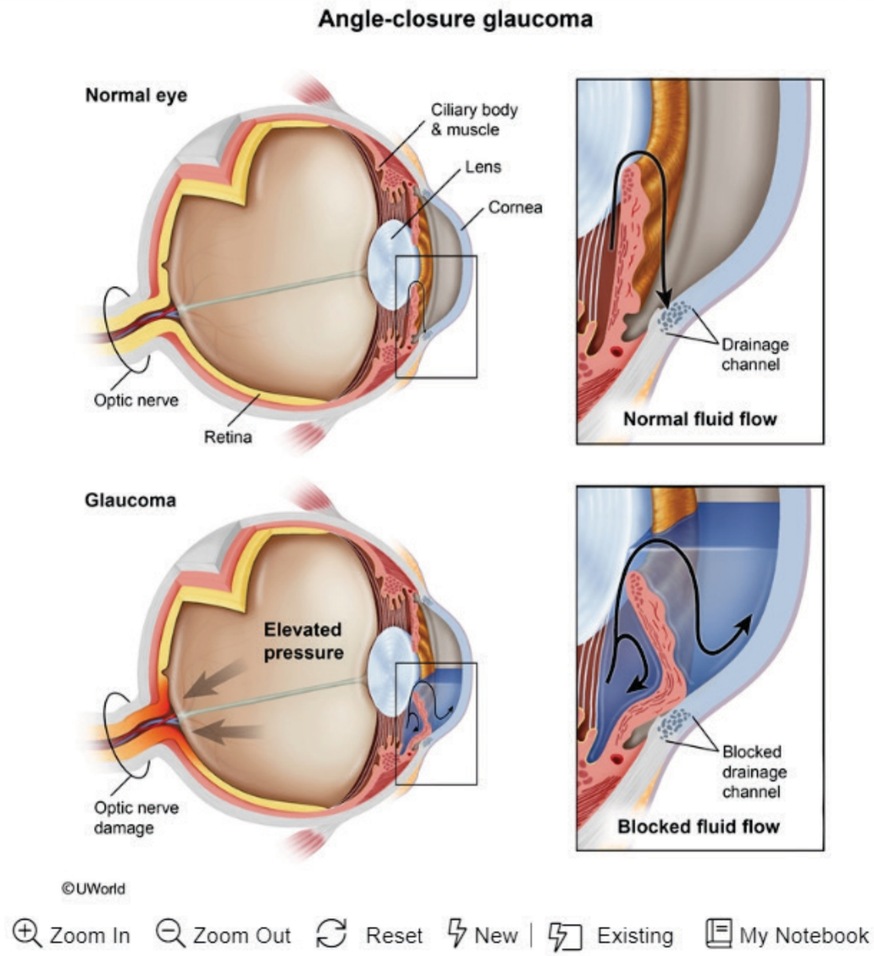
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Educational objective:
Carbonic anhydrase inhibitors (eg, acetazolamide) reduce intraocular pressure in patients with glaucoma by reducing production of aqueous humor. Carbonic anhydrase is also found in the renal proximal tubule, where it catalyzes reactions necessary for bicarbonate (HCO_3) reabsorption. Acetazolamide therefore induces a mild diuresis with increased urine pH and resulting mild metabolic acidosis.

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D. Distal convoluted tube:
Thiazide diuretics

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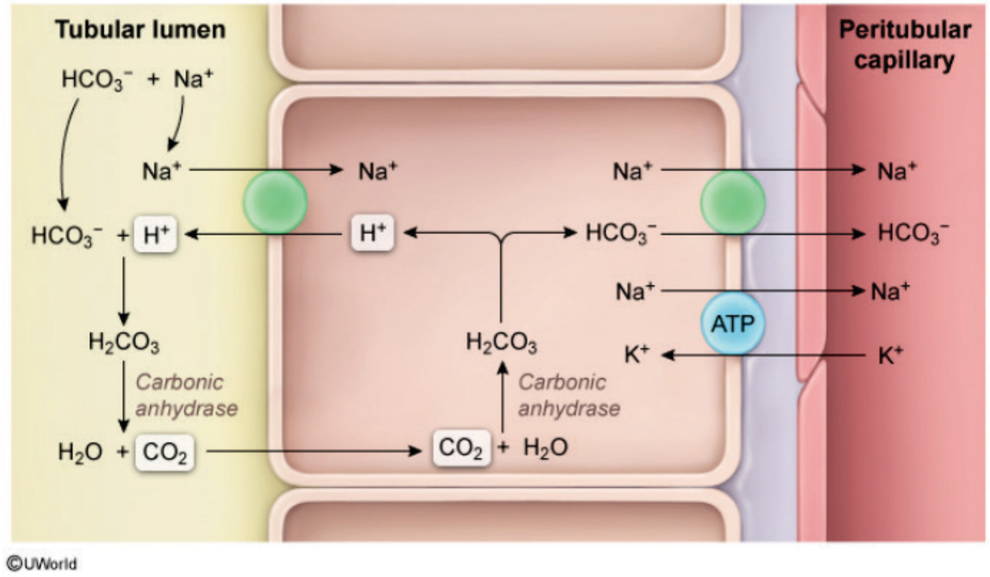
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(Choice C) Loop diuretics (eg, furosemide) are the mainstay of diuretic therapy for heart failure because they

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D. Distal convoluted tube:
Thiazide diuretics

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A 56-year-old man with type 2 diabetes mellitus, hypertension, and chronic kidney disease is found to have a persistently elevated serum potassium level. He takes lisinopril. Blood pressure is 130/90 mm Hg. Physical examination shows no abnormalities. The patient is prescribed patiromer therapy. Which of the following best describes the mechanism of action of this medication?

- A. Activates the Na^+-K^+-ATPase pump in skeletal muscle
- B. Antagonizes aldosterone effect on renal tubules
- C. Antagonizes membrane effects of hyperkalemia
- D. Exchanges calcium for potassium in the intestine
- E. Increases renal excretion of potassium

Submit

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- A. Activates the Na^+-K^+-ATPase pump in skeletal muscle (4%)
- ✗ B. Antagonizes aldosterone effect on renal tubules (6%)
- C. Antagonizes membrane effects of hyperkalemia (10%)
- ✓ D. Exchanges calcium for potassium in the intestine (40%)
- E. Increases renal excretion of potassium (37%)

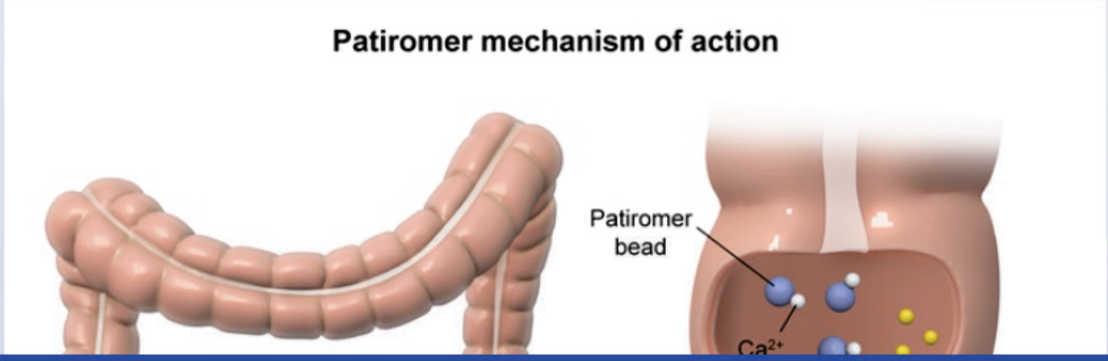
Incorrect
Correct answer
D

40%
Answered correctly

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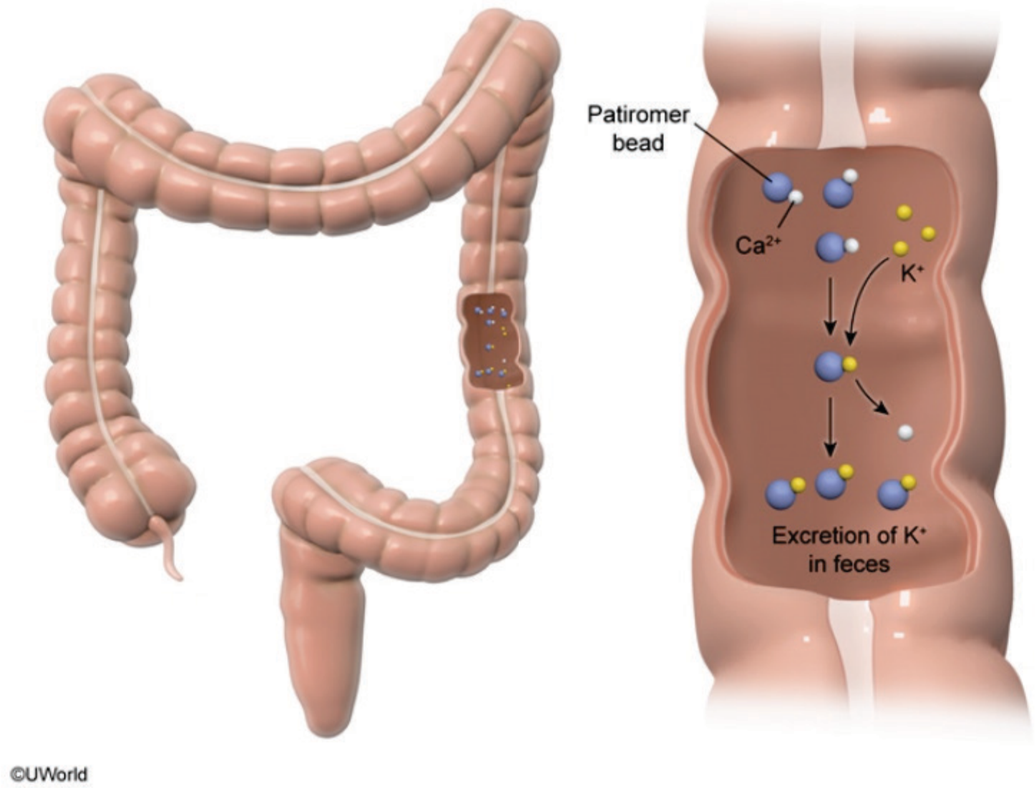
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Hyperkalemia is a common complication of chronic kidney disease that results from impaired potassium excretion. Medications that inhibit the renin-angiotensin-aldosterone system (eg, ACE inhibitors, mineralocorticoid blockers) can also worsen hyperkalemia, often limiting their use in this population.

Patiromer is a nonabsorbable cation exchange resin that **binds colonic potassium** in **exchange for calcium**, trapping potassium within the resin where it is then excreted in the feces. It is often used for treatment of chronic hyperkalemia. However, onset of action takes several hours, so it is not recommended as monotherapy in acute hyperkalemia. Adverse effects include gastrointestinal disturbance (eg, diarrhea), hypokalemia, hypercalcemia (due to luminal exchange of calcium), and hypomagnesemia (due to off-target binding of other positive ions). Patiromer may also bind certain medications (eg, ciprofloxacin, levothyroxine).

Sodium zirconium cyclosilicate is another nonabsorbable cation exchange resin that binds intestinal potassium in exchange for sodium and hydrogen. It is more selective for potassium and does not interfere with absorption of magnesium or other medications. However, the increased sodium load may be problematic for patients sensitive to exogenous sodium (eg, cirrhosis, congestive heart failure).

(Choice A) Beta-2 agonists and insulin increase the activity of the Na^+-K^+-ATPase in skeletal muscles, which transiently increases intracellular translocation of potassium. These medications are used in the treatment of acute, severe hyperkalemia but do not have a sustained potassium-lowering effect.

(Choice B) Mineralocorticoid blockers (eg, spironolactone, eplerenone) antagonize the effects of aldosterone in the renal tubules. This leads to increased reabsorption of potassium, which will worsen hyperkalemia.

(Choice C) Calcium gluconate antagonizes the effects of hyperkalemia on cell membrane potential and is used in severe hyperkalemia to stabilize cardiac myocytes and prevent arrhythmias. It does not lower serum potassium levels.

(Choice E) Loop diuretics (eg, furosemide) increase renal excretion of potassium. Patiromer inhibits dietary potassium absorption and therefore decreases the total amount of renally excreted potassium.

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Educational objective:
Patiromer is a nonabsorbable cation exchange resin used to treat hyperkalemia. It binds colonic potassium in exchange for calcium, trapping potassium within the resin where it is then excreted in the feces. Adverse effects include diarrhea, hypokalemia, hypercalcemia, and hypomagnesemia.

Pharmacology Renal, Urinary Systems & Electrolytes Hyperkalemia

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A 21-year-old woman with type 1 diabetes mellitus comes to the office for a follow-up appointment. She has been using daily long-acting and short-acting insulin injections from the time she was diagnosed 6 years ago. The patient was seen by her ophthalmologist 2 weeks ago and had no signs of diabetic retinopathy. She eats a balanced diet and jogs every morning for 40 minutes. On examination, the skin of her extremities is intact and peripheral pulses are palpable. Sensory examination shows normal pinprick, vibration, and temperature sensation in her lower extremities. Laboratory evaluation shows normal renal function and lipid profile. The patient's hemoglobin A1c level is 7%. Screening for early-stage diabetic nephropathy in this patient would best be accomplished by measuring the urinary concentration of which of the following substances?

- A. Albumin
- B. Glucose
- C. Ketones
- D. Red blood cell casts
- E. Tubular protein
- F. Waxy casts

Submit

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- ✓ A. Albumin (79%)
- ✗ B. Glucose (9%)
- C. Ketones (2%)
- D. Red blood cell casts (0%)
- E. Tubular protein (6%)
- F. Waxy casts (2%)

Incorrect
Correct answer
A

79%
Answered correctly

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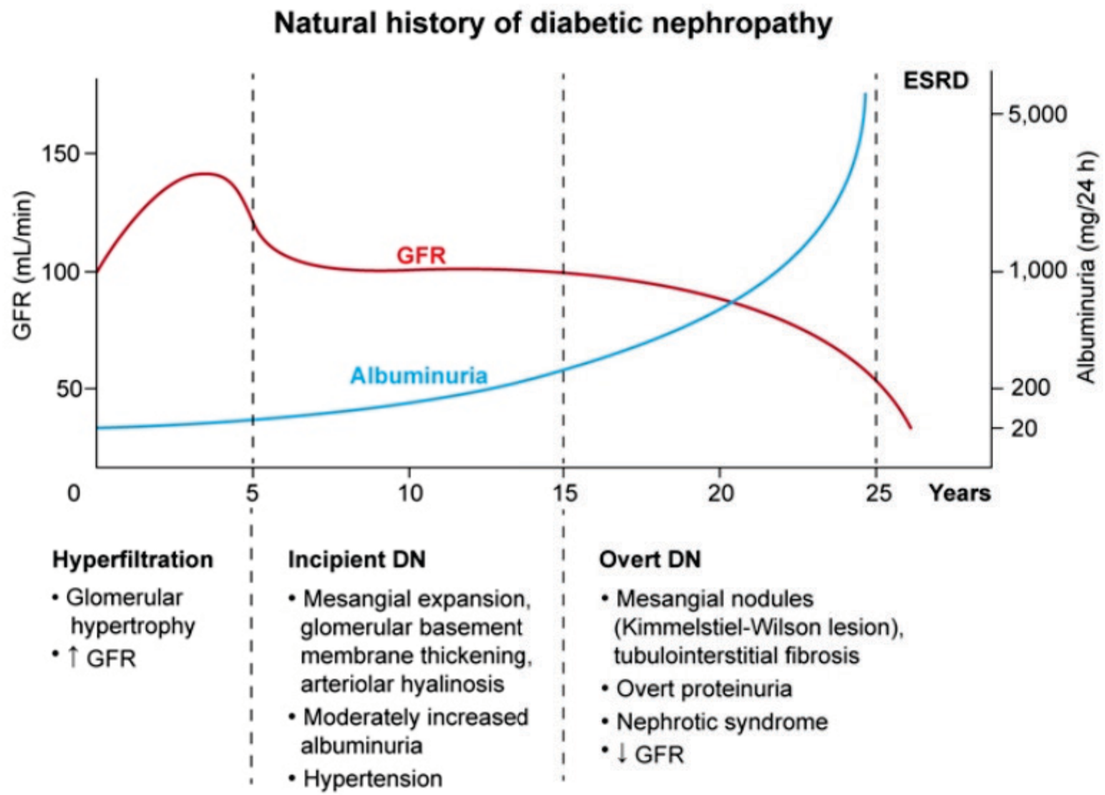


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Correct answer
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Diabetic nephropathy (DN) is the most common cause of end-stage renal disease in the United States. It occurs in both types 1 and 2 diabetes. The earliest morphological change is glomerular basement membrane thickening

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Diabetic nephropathy (DN) is the most common cause of end-stage renal disease in the United States. It occurs in both types 1 and 2 diabetes. The earliest morphological change is glomerular basement membrane thickening with mesangial matrix expansion. Normally, the glomerular basement membrane has negatively charged heparan sulfate moieties that form a charge barrier preventing leakage of negatively charged proteins (eg, albumin) into the Bowman capsule. In diabetes, there is progressive loss of this negative charge due to upregulation of heparanase expression by renal epithelial cells, leading to leakage of albumin and other plasma proteins.

In the initial stages of DN, only small amounts of albumin (30-300 mg/day; ie, **moderately increased albuminuria**) are lost but can be detected with an albumin-specific urine assay (regular dipstick urinalysis has low sensitivity and is not recommended). Early administration of **ACE inhibitors** in patients with diabetes and moderately increased albuminuria can reduce urinary albumin excretion and slow progression to overt DN.

(Choice B) Glycosuria is seen at blood glucose levels >200-300 mg/dL due to saturation of renal glucose transporters. Glycosuria reflects poor glycemic control but does not correlate with the degree of renal damage in DN.

(Choice C) Ketonuria occurs in starvation and in conditions that cause ketoacidosis, such as insufficient insulin administration in patients with type 1 diabetes mellitus. It is usually a transient phenomenon that corrects with treatment of the ketoacidosis.

(Choice D) Red blood cell casts are a sign of glomerular bleeding, such as in glomerulonephritis (eg, poststreptococcal glomerulonephritis). Diabetes mellitus usually causes a nephrotic syndrome with proteinuria and a bland urine sediment.

(Choice E) Low-molecular-weight proteins (eg, beta-2 microglobulin, immunoglobulin light chains) are normally filtered by the glomerulus and reabsorbed in the renal tubules. Damage to the tubular cells can cause loss of these tubular proteins in urine. Ischemic tubular damage may be seen in advanced DN.

(Choice F) Waxy casts are shiny, translucent structures formed in the dilated tubules of enlarged nephrons that undergo compensatory hypertrophy in response to reduced renal mass. They indicate advanced renal disease

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(Choice F) Waxy casts are shiny, translucent structures formed in the dilated tubules of enlarged nephrons that undergo compensatory hypertrophy in response to reduced renal mass. They indicate advanced renal disease (chronic renal failure).

Educational objective:
Moderately increased albuminuria (urine albumin 30-300 mg/day) is the earliest manifestation of diabetic nephropathy. Screening for diabetic nephropathy is best achieved using an albumin-specific urine assay (regular dipstick urinalysis has low sensitivity).

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A 62-year-old man comes to the office due to poorly localized, intermittent abdominal pain that is triggered by eating and slowly subsides over the ensuing several hours. The patient has also lost 4.5 kg (10 lb) over the past 2 months. He has a history of hypertension and hyperlipidemia and has smoked a pack of cigarettes daily for 40 years. Blood pressure is 175/105 mm Hg and pulse is 70/min and regular. The abdomen is soft and nontender. CT scan of the abdomen reveals the renal findings shown in the image below.



This patient most likely suffers from which of the following conditions?

- A. Acute glomerulonephritis
- B. Acute pyelonephritis
- C. Amyloidosis
- D. Fanconi syndrome

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A 62-year-old man comes to the office due to poorly localized, intermittent abdominal pain that is triggered by eating. He has had this pain for several months. He has had a similar episode of pain once a year for the past 3 years. A CT s

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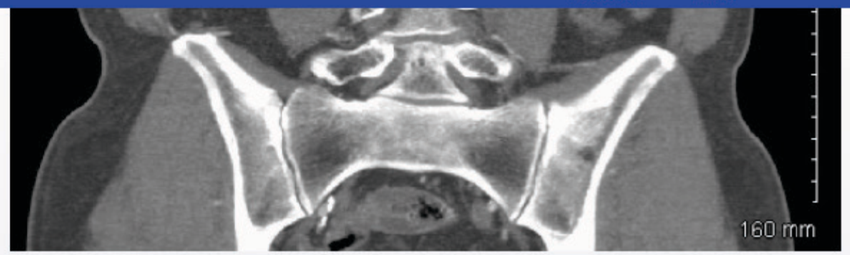


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D. Fanconi syndrome

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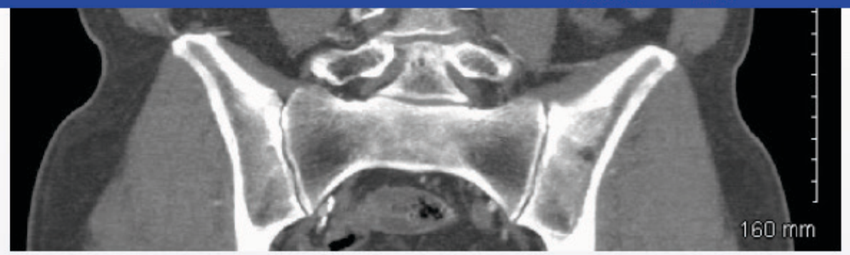


This patient most likely suffers from which of the following conditions?

- A. Acute glomerulonephritis
- B. Acute pyelonephritis
- C. Amyloidosis
- D. Fanconi syndrome
- E. Hemolytic uremic syndrome
- F. Hypersensitivity interstitial nephritis
- G. Ischemic tubular necrosis
- H. Myeloma kidney
- I. NSAID-associated nephropathy
- J. Papillary necrosis
- K. Renal artery stenosis
- L. Urate nephropathy

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This patient most likely suffers from which of the following conditions?

- A. Acute glomerulonephritis (0%)
- ✗ B. Acute pyelonephritis (1%)
- C. Amyloidosis (2%)
- D. Fanconi syndrome (2%)
- E. Hemolytic uremic syndrome (0%)
- F. Hypersensitivity interstitial nephritis (0%)
- G. Ischemic tubular necrosis (5%)
- H. Myeloma kidney (9%)
- I. NSAID-associated nephropathy (3%)
- J. Papillary necrosis (6%)
- ✓ K. Renal artery stenosis (62%)
- L. Urate nephropathy (3%)

Incorrect
Correct answer
K

62%
Answered correctly

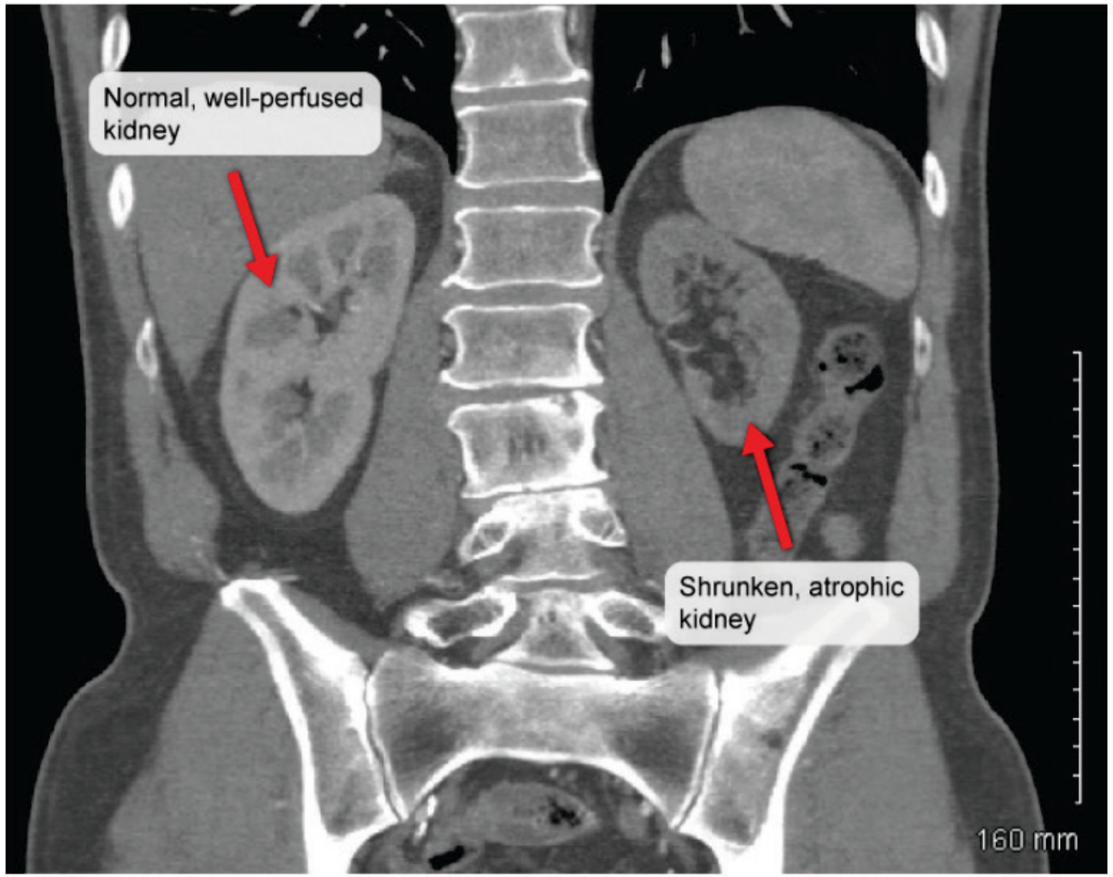
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L. Urate nephropathy (3%)

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This patient has postprandial pain and a 4.5-kg (10-lb) weight loss as well as multiple risk factors for **atherosclerosis** (eg, advanced age, hypertension, smoking). This presentation is highly suggestive of **chronic mesenteric (intestinal) ischemia**. Atherosclerotic narrowing of the abdominal (superior mesenteric or celiac) arteries results in reduced blood flow to the intestine; during periods of high metabolic requirement (ie, after eating), patients can develop "intestinal angina" (dull, cramping abdominal pain that resolves 2-3 hours after meals).

Atherosclerosis is a multiorgan disease, and patients often have involvement of other major vessels, including coronary artery disease, carotid stenosis, peripheral vascular disease, and **renal artery stenosis** (RAS). Atherosclerotic RAS often becomes apparent at age 60-70 and is typically associated with prominent atherosclerotic plaques at the junction of the aorta and the renal artery. Less frequently, nonatherosclerotic RAS occurs secondary to fibromuscular dysplasia, a disease that affects predominantly younger women and causes narrowing of multiple renal artery segments (string-of-beads appearance).

In **unilateral RAS**, chronic ischemia atrophies the affected kidney while the contralateral kidney undergoes compensatory hypertrophy, leading to **renal size discrepancy**, as seen in this patient. Renal hypoperfusion also activates the renin-angiotensin-aldosterone system, resulting in hypertension that is often refractory to medications. Abdominal and flank bruits are highly suggestive of RAS. Light microscopy of the atrophic kidney reveals tubular atrophy with decreased tubular epithelial size, patchy inflammation, and tubulointerstitial and glomerular fibrosis.

Educational objective:
Marked unilateral kidney atrophy is suggestive of renal artery stenosis. It occurs in elderly individuals due to atherosclerotic narrowing of the renal artery and is often seen in association with other atherosclerotic risk factors or diseases (eg, chronic mesenteric ischemia, coronary artery disease, peripheral vascular disease). Hypertension and abdominal and flank bruits are often present.

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A 7-year-old boy is brought to the office by his mother due to facial puffiness that is especially noticeable in the morning. He has a history of mild, intermittent asthma that is well controlled with albuterol as needed. Temperature is 36.1 C (97 F), blood pressure is 98/62 mm Hg, and pulse is 89/min and regular. Physical examination shows bilateral lower extremity pitting edema. Nephrotic-range proteinuria consisting mainly of albumin is revealed on urinalysis. Which of the following mechanisms is the most likely cause of this patient's abnormal laboratory findings?

- A. Impaired tubular reabsorption of filtered proteins
- B. Increased filtration of plasma proteins
- C. Inflammation of the urinary tract
- D. Necrosis of skeletal muscle fibers
- E. Overproduction of low-molecular-weight proteins

Submit

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- A. Impaired tubular reabsorption of filtered proteins (12%)
- ✓ B. Increased filtration of plasma proteins (82%)
- C. Inflammation of the urinary tract (1%)
- D. Necrosis of skeletal muscle fibers (0%)
- E. Overproduction of low-molecular-weight proteins (2%)

Correct

82%
Answered correctly

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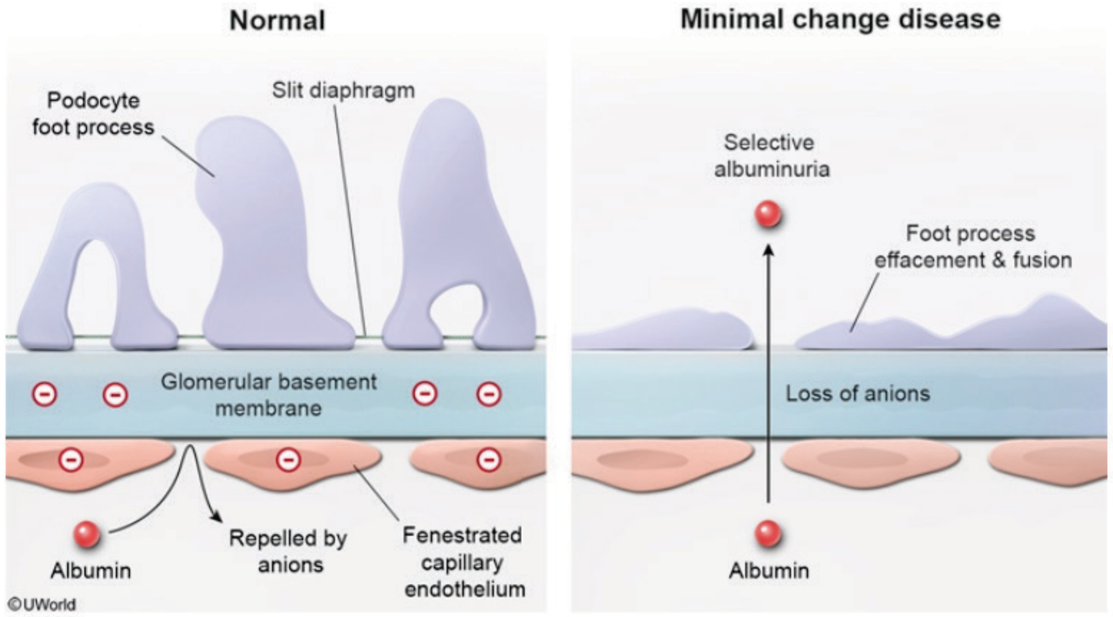
Explanation



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abnormal laboratory findings?

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This child with volume overload (eg, facial puffiness, edema) and nephrotic-range proteinuria consisting mainly of albumin most likely has **minimal change disease**, the most common cause of **nephrotic syndrome** in **children**.

Renal filtration of macromolecules is mediated by the glomerular filtration barrier, which consists of fenestrated endothelium, the glomerular basement membrane (GBM), and podocytes. This barrier has selective permeability based on molecular size and charge. Size selectivity is dependent on pores in the GBM and the thin membrane between the foot processes of podocytes (slit diaphragm). Charge selectively is reliant on polyanions (eg, heparan sulfate) on the GBM and endothelial cells, which repel negatively charged molecules such as albumin.

Albumin is small enough to fit through pores in the GBM and slit diaphragms, but it is not normally filtered through the glomerular filtration barrier due to its negative charge. In patients with minimal change disease, systemic T-cell dysfunction leads to the production of glomerular permeability factor, a cytokine that causes **podocyte foot process fusion** and decreases the anionic properties of the GBM. **Loss of negative charge** leads to increased filtration of negatively charged plasma proteins and selective loss of albumin in the urine (**selective albuminuria**).

(Choice A) Low-molecular-weight proteins (eg, beta-2 microglobulin, immunoglobulin light chains) are normally filtered by the glomerulus and almost completely reabsorbed in the proximal tubule. Tubular proteinuria occurs when proximal tubular function is disrupted (eg, tubulointerstitial nephritis).

(Choice C) Inflammation of the urinary tract (eg, due to infection) causes production of a proteinaceous inflammatory exudate that can leak into the urine. However, the proteinuria is generally mild (non-nephrotic range) and often accompanied by leukocyturia.

(Choices D and E) Overflow proteinuria can occur if a particular protein is produced in excess amounts, leading to increased glomerular filtration and excretion of that protein. This can occur with excess light chain production in multiple myeloma or in rhabdomyolysis, in which necrosis of the skeletal muscle leads to increased excretion of myoglobin in the urine.

Educational objective:

Minimal change disease is the most common cause of nephrotic syndrome in children. Systemic T-cell dysfunction

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endothelium, the glomerular basement membrane (GBM), and podocytes. This barrier has selective permeability based on molecular size and charge. Size selectivity is dependent on pores in the GBM and the thin membrane between the foot processes of podocytes (slit diaphragm). Charge selectively is reliant on polyanions (eg, heparan sulfate) on the GBM and endothelial cells, which repel negatively charged molecules such as albumin.

Albumin is small enough to fit through pores in the GBM and slit diaphragms, but it is not normally filtered through the glomerular filtration barrier due to its negative charge. In patients with minimal change disease, systemic T-cell dysfunction leads to the production of glomerular permeability factor, a cytokine that causes **podocyte foot process fusion** and decreases the anionic properties of the GBM. **Loss of negative charge** leads to increased filtration of negatively charged plasma proteins and selective loss of albumin in the urine (**selective albuminuria**).

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(Choice C) Inflammation of the urinary tract (eg, due to infection) causes production of a proteinaceous inflammatory exudate that can leak into the urine. However, the proteinuria is generally mild (non-nephrotic range) and often accompanied by leukocyturia.

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Educational objective:
Minimal change disease is the most common cause of nephrotic syndrome in children. Systemic T-cell dysfunction leads to the production of glomerular permeability factor, which causes podocyte foot process fusion and decreases the anionic properties of the glomerular basement membrane. The loss of negative charge leads to selective albuminuria.

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A 25-year-old primigravida at 18 weeks gestation comes to the office with her husband for routine follow-up. She reports no concerns, and abdominal examination shows normal fundal height. Anatomy ultrasound of the fetus shows male sex. The fetus' kidneys appear fused at the lower poles and are located low in the abdomen. The remainder of the ultrasound is unremarkable. The couple asks about implications of these findings and the ways they will affect the child after birth. Which of the following is the best response?

A. "Many children with this disorder develop kidney dysfunction that progresses to end-stage renal disease, so we will need to follow up closely for this."

B. "Patients with these findings are at an increased risk for forming cerebral aneurysms over their lifetime, so periodic screening is recommended."

C. "The majority of patients with this developmental anomaly are asymptomatic, but there is an increased risk for urinary tract infections."

D. "These findings are part of a developmental sequence that can lead to impaired lung development with potential respiratory distress at delivery."

E. "This genetic condition is associated with varying degrees of liver disease, which warrants periodic imaging of the liver."

Submit

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- A. "Many children with this disorder develop kidney dysfunction that progresses to end-stage renal disease, so we will need to follow up closely for this." (10%)
- B. "Patients with these findings are at an increased risk for forming cerebral aneurysms over their lifetime, so periodic screening is recommended." (2%)
- ✓ C. "The majority of patients with this developmental anomaly are asymptomatic, but there is an increased risk for urinary tract infections." (76%)
- D. "These findings are part of a developmental sequence that can lead to impaired lung development with potential respiratory distress at delivery." (9%)
- E. "This genetic condition is associated with varying degrees of liver disease, which warrants periodic imaging of the liver." (1%)

Correct

76%
Answered correctly

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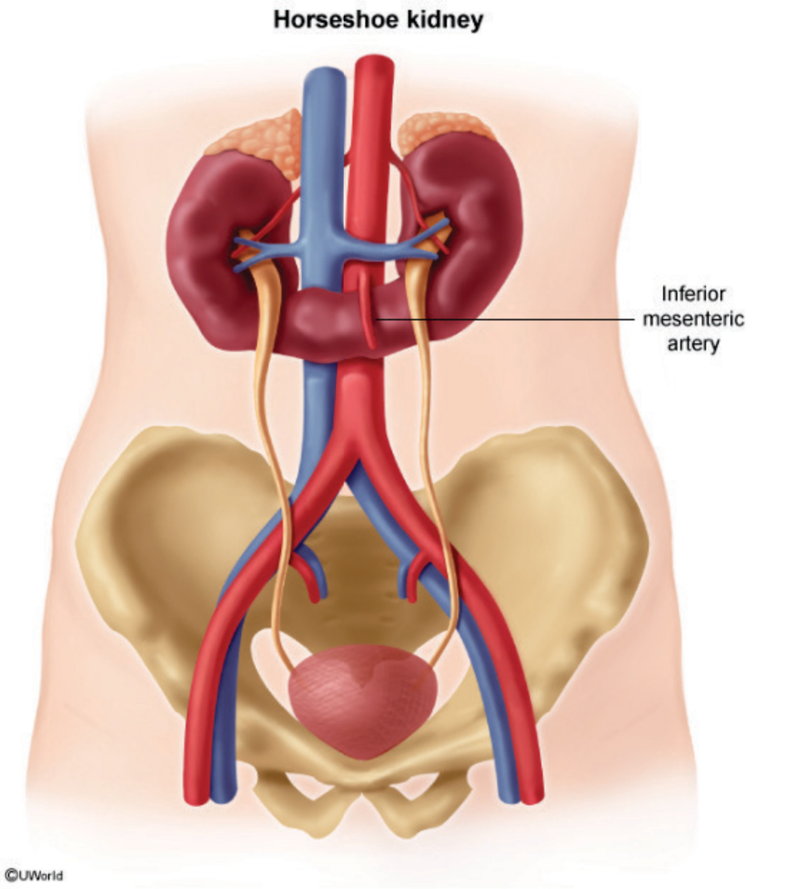
Explanation

Horseshoe kidney

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increased risk for urinary tract infections."

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This patient's prenatal ultrasound reveals a fetus with **fusion of the inferior kidney poles**, a congenital anomaly known as **horseshoe kidney**.

Pathophysiology of horseshoe kidney involves abnormal migration of the right and left metanephric blastema (from which the renal parenchyma is derived), leading to fusion of the developing inferior poles. The kidneys' physiologic ascent into the abdomen is limited due to the fused parenchyma (isthmus), which is mechanically restricted by the overlying inferior mesenteric artery (IMA) at its origin from the aorta (**low-lying position**).

Most patients with horseshoe kidney and its associated anatomic abnormalities are **asymptomatic**. However, in some patients, the abnormal position of the kidney and ureters may lead to intermittent ureteropelvic junction obstruction and urinary stasis, which increase the risk for **nephroliths** and **urinary tract infections**.

(Choices A and D) Patients with autosomal recessive polycystic kidney disease (ARPKD) often have decreased renal function in utero, which may lead to oligohydramnios and pulmonary hypoplasia (Potter sequence). ARPKD also frequently leads to end-stage kidney disease, warranting close monitoring. However, prenatal ultrasound would reveal large, hyperechogenic kidneys with many tiny cysts in contrast to this patient's fused kidney.

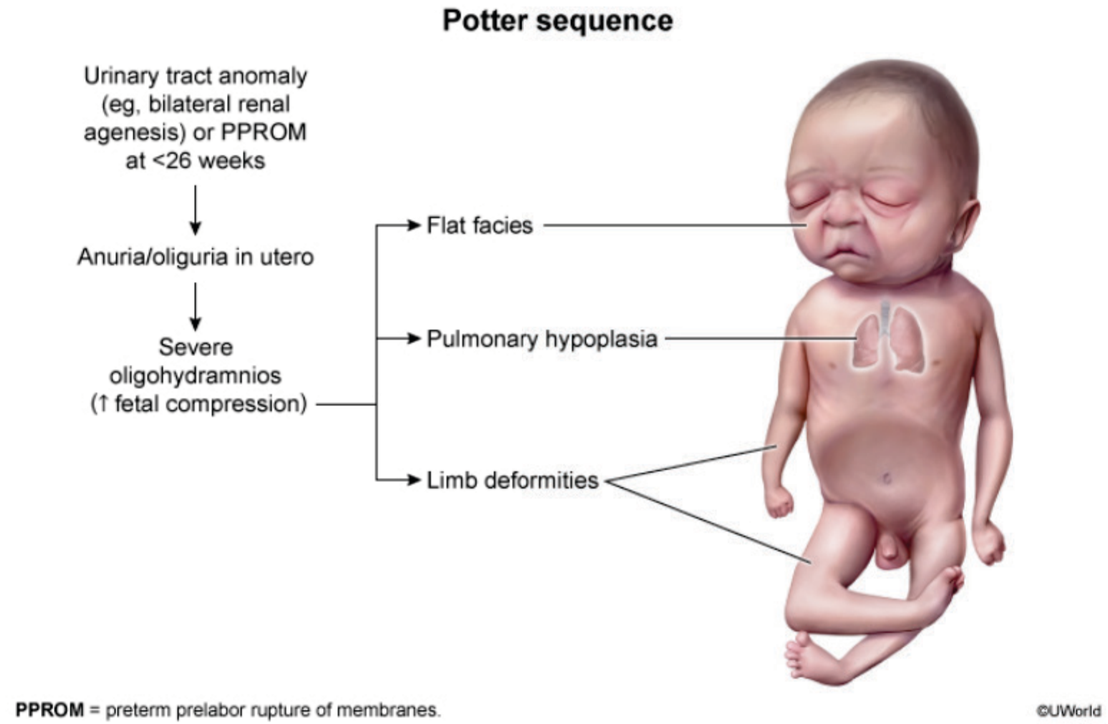
(Choices B and E) Both ARPKD and autosomal dominant polycystic kidney disease (ADPKD) are associated with hepatic manifestations, specifically bile duct dysgenesis and fibrosis in ARPKD and asymptomatic cysts in ADPKD. Patients with ADPKD are also at risk for cerebral aneurysms due to abnormal gene expression in vascular smooth muscle cells. Horseshoe kidney is not associated with extrarenal manifestations (eg, liver disease, cerebral aneurysms).

Educational objective:
Horseshoe kidney is a congenital anomaly in which the inferior poles of the developing kidney fuse in utero. Most patients remain asymptomatic but are at increased risk for recurrent nephroliths and urinary tract infections due to the abnormal orientation and positioning of the kidney.

Embryology Renal, Urinary Systems & Electrolytes Congenital anomalies of kidney and urinary tract

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A 65-year-old hospitalized man is evaluated for decreased urine output and increased serum creatinine. The patient was admitted for 3-vessel coronary artery disease and underwent coronary artery bypass grafting surgery yesterday. Other medical conditions include type 2 diabetes mellitus and hypertension. He received a dose of intravenous vancomycin prior to the surgery for prophylaxis of surgical infection. The patient has also been receiving 100 mL/hour of intravenous normal saline for the past 24 hours. He is afebrile. Blood pressure is 130/80 mm Hg and pulse is 80/min. Examination shows bibasilar crackles. The abdomen is soft. Urine output over the past 6 hours is 100 mL. Laboratory results are as follows:

	Day of admission	Today
Blood urea nitrogen	20 mg/dL	35 mg/dL
Serum creatinine	1.3 mg/dL	2.5 mg/dL

Urine sediment microscopy is shown in the exhibit. Which of the following is the most likely cause of this patient's current condition?

- A. Crystal obstruction in tubules
- B. Drug toxicity to renal tubules
- C. Glomerulonephritis
- D. Interstitial inflammation
- E. Ischemic tubular necrosis
- F. Prerenal azotemia

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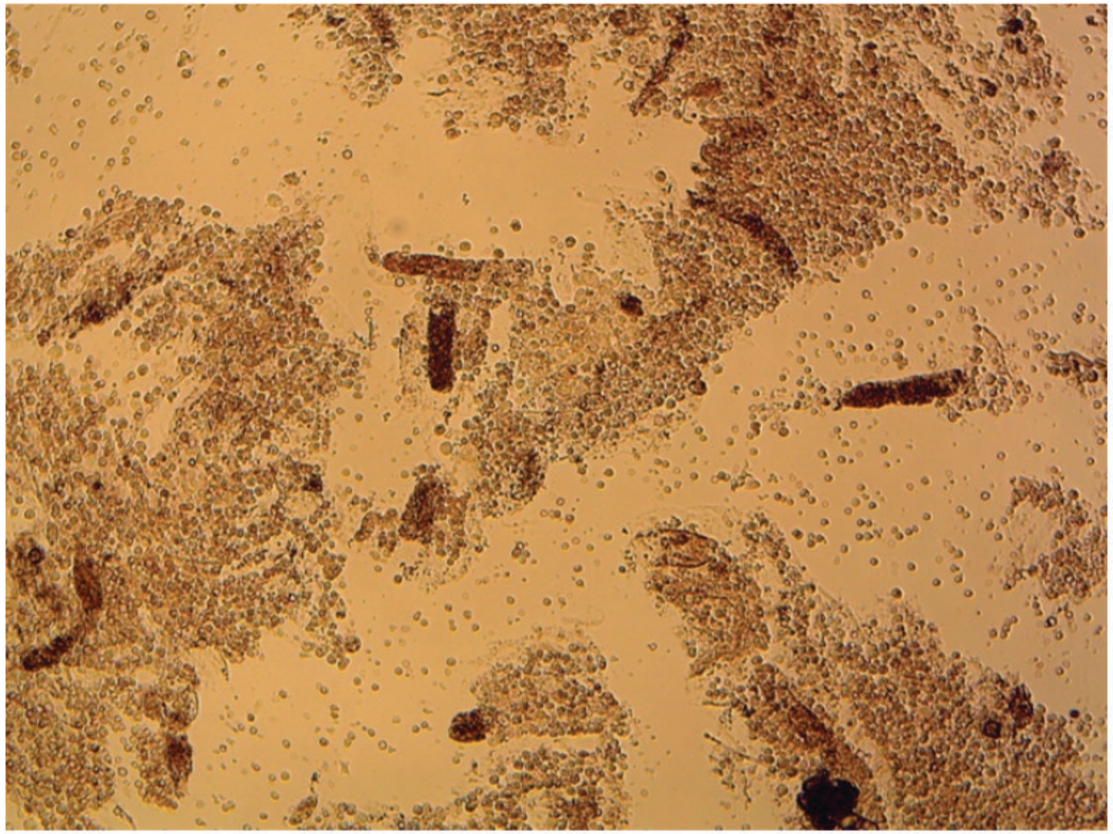
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	Day of admission	Today
Blood urea nitrogen	20 mg/dL	35 mg/dL
Serum creatinine	1.3 mg/dL	2.5 mg/dL

Urine sediment microscopy is shown in the exhibit. Which of the following is the most likely cause of this patient's current condition?

- A. Crystal obstruction in tubules (2%)
- B. Drug toxicity to renal tubules (40%)
- C. Glomerulonephritis (1%)
- ✗ D. Interstitial inflammation (3%)
- ✓ E. Ischemic tubular necrosis (48%)
- F. Prerenal azotemia (4%)

Incorrect
Correct answer
E

48%
Answered correctly

11 secs
Time Spent

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Urinary casts	Composition	Associated conditions
Hyaline	• Tamm-Horsfall protein	• Nonspecific, concentrated urine
Fatty	• Lipid droplets	• Nephrotic syndrome
Waxy	• Degenerated hyaline cast	• Chronic kidney disease
Granular (muddy brown)	• Sloughed tubular epithelial cells with pigmented granules	• Acute tubular necrosis
WBC	• White blood cells	• Pyelonephritis, interstitial nephritis
RBC	• Red blood cells	• Glomerulonephritis

This patient with **acute kidney injury** has muddy brown casts on urine microscopy; in the setting of recent major surgery this presentation suggests **acute tubular necrosis** (ATN) due to **intraoperative renal ischemia**. Surgeries complicated by significant blood loss or those requiring the use of cardiopulmonary bypass (eg, coronary artery bypass grafting) or aortic clamping can cause renal hypoperfusion. The risk is increased in the elderly and those with a history of chronic kidney disease, diabetes, or congestive heart failure.

ATN is characterized by the presence of muddy brown granular casts composed of sloughed renal tubular epithelial cells. Patients have increased serum creatinine, **blood urea nitrogen/ creatinine ratio <20:1** (indicating intrinsic renal pathology), and oliguria (low urine output). Histologically, flattened tubular epithelial cells with cellular

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(Choice A) Crystalline-induced kidney injury most commonly occurs from acyclovir or sulfonamide (eg, sulfadiazine) usage. Urinalysis demonstrates needle or rosette-shaped crystals. Vancomycin is not associated with crystal formation.

(Choice B) Vancomycin can cause ATN, but this typically occurs after a prolonged course (days). It is highly unlikely that a single dose would cause ATN.

(Choice C) Glomerulonephritis can cause acute kidney injury, but hematuria and red blood cell casts are expected on urinalysis. In addition, patients are typically hypertensive.

(Choice D) Acute interstitial nephritis can occur after exposure to new drugs, particularly antibiotics and diuretics. However, white blood cells and white cell casts are expected on urinalysis, and patients often have fever and rash.

(Choice F) Prerenal azotemia occurs from less significant renal hypoperfusion without renal ischemia (eg, dehydration). Urinalysis reveals hyaline casts (reflecting concentrated urine) and the blood urea nitrogen/creatinine ratio is elevated (>20:1).

Educational objective:
Surgeries complicated by significant blood loss or those requiring the use of cardiopulmonary bypass or clamping

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Educational objective:
Surgeries complicated by significant blood loss or those requiring the use of cardiopulmonary bypass or clamping of the aorta can cause sustained renal hypoperfusion and result in acute tubular necrosis (ATN). ATN presents with oliguria, increased serum creatinine, and blood urea nitrogen/creatinine ratio <20:1. Urinalysis is characterized by muddy brown granular casts composed of sloughed renal tubular epithelial cells.

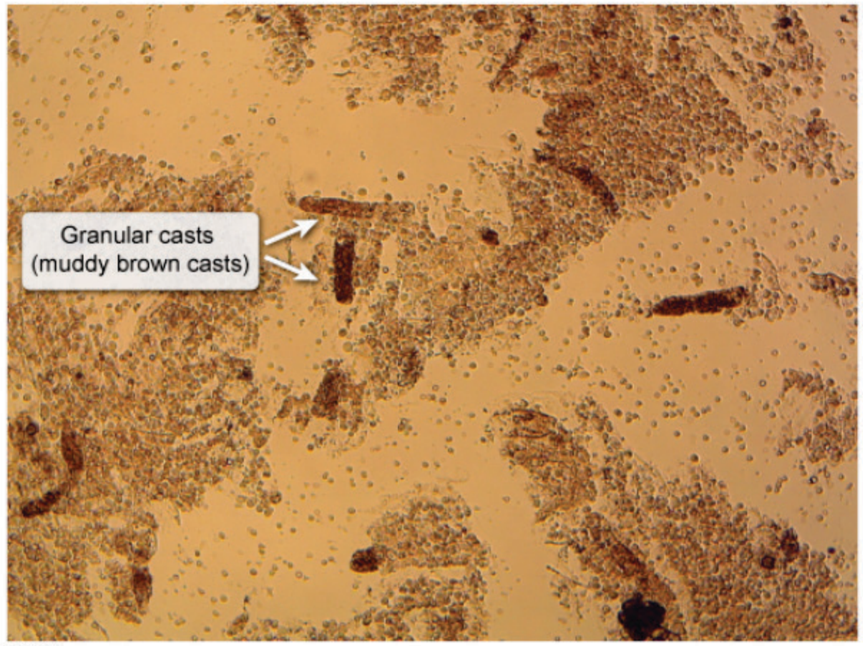
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WBC	• White blood cells

nephritis

Exhibit Display

Acute tubular necrosis



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dehydration). Urinalysis reveals hyaline casts (reflecting concentrated urine) and the blood urea

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A 44-year-old woman comes to the office for a follow-up appointment. Six months earlier, the patient was diagnosed with essential hypertension; she has followed dietary and exercise recommendations since then. At a follow-up visit 3 months ago, she reported episodic headaches due to migraines. Her blood pressure at that visit was 145/92 mm Hg. Antihypertensive therapy with a beta blocker was started due to its beneficial effect on migraine prophylaxis. Now, 3 months later, the patient's blood pressure has decreased to 120/80 mm Hg. She is compliant with her medication and has had no serious adverse effects. Which of the following is the most likely combination of changes in response to this patient's treatment (AT = Angiotensin)?

	Renin	AT I	AT II	Aldosterone	Bradykinin
○ A.	↓	↓	↓	↓	No change
○ B.	↑	↓	↓	↓	No change
○ C.	↑	↑	↓	↓	↓
○ D.	↑	↑	↓	↓	↑
○ E.	↑	↑	↑	↓	No change
○ F.	↑	↑	↑	↑	No change

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	Renin	AT I	AT II	Aldosterone	Bradykinin	
✓ A.	↓	↓	↓	↓	No change	(73%)
B.	↑	↓	↓	↓	No change	(3%)
C.	↑	↑	↓	↓	↓	(2%)
D.	↑	↑	↓	↓	↑	(5%)
E.	↑	↑	↑	↓	No change	(3%)
F.	↑	↑	↑	↑	No change	(11%)

Correct

73% Answered correctly

03 secs Time Spent

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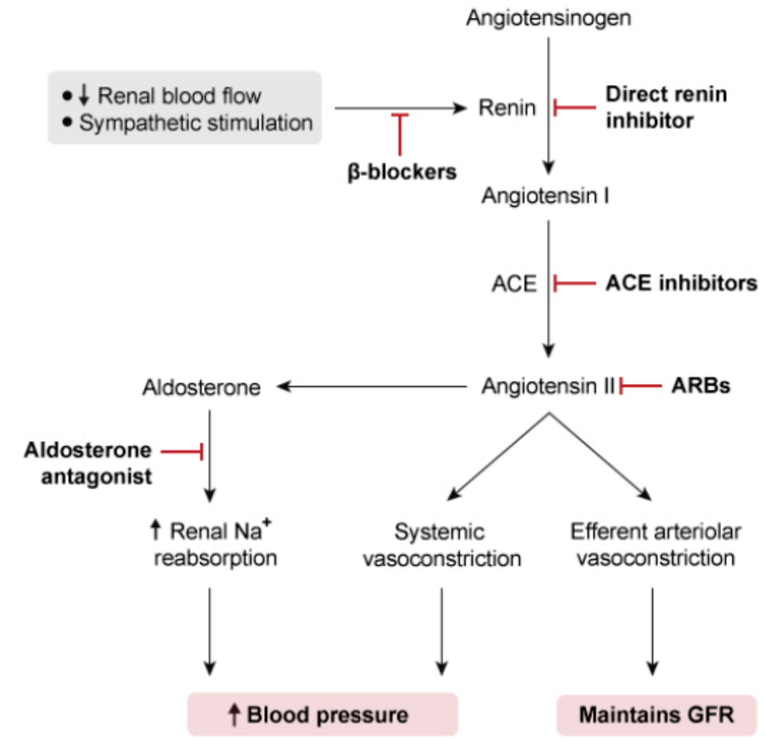
Explanation

Renin-angiotensin-aldosterone system &

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Renin-angiotensin-aldosterone system & antihypertensives



GFR = glomerular filtration rate.

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The renin-angiotensin-aldosterone system (RAAS) is the most important neurohormonal system regulating sodium/fluid balance and arterial blood pressure in the body. Regulation of the RAAS involves 3 major components: macula densa (distal tubule sodium sensor), intrarenal baroreceptors, and beta-adrenergic receptors. Beta-adrenergic regulation is mediated through sympathetic stimulation of **beta-1 receptors** located on juxtaglomerular cells, which stimulate the release of renin.

Beta-adrenergic antagonists inhibit renin release, which in turn reduces the conversion of angiotensinogen to angiotensin I and reduces the levels of angiotensin II and aldosterone. This effect on the RAAS is only partially responsible for beta blocker effects on blood pressure, and antihypertensive efficacy of beta blockers weakly correlates with plasma renin levels. Beta blockers have no effect on ACE activity and, therefore, do not affect bradykinin levels.

(Choice B) Direct renin inhibitors (aliskiren) block the conversion of angiotensinogen to angiotensin I, which leads to reduced levels of angiotensin I and II and aldosterone. Plasma renin concentration is increased via suppression of the inhibitory feedback loop.

(Choices C and D) ACE inhibitors prevent the conversion of angiotensin I to angiotensin II and lead to decreased levels of angiotensin II and aldosterone, along with increased plasma renin activity and angiotensin I levels via inhibition of negative feedback. ACE is also a kininase and normally degrades bradykinin in the body. Therefore, ACE inhibitors lead to increased levels of bradykinin, which is responsible for the coughing seen in treated patients.

(Choice E) Angiotensin II receptor blockers (ARBs) block the action of angiotensin II on angiotensin (AT1) receptors, which leads to increased levels of renin and angiotensin I and II. ARBs have no effect on bradykinin levels.

(Choice F) Aldosterone antagonists (spironolactone, eplerenone) compete with aldosterone for the receptor sites in the distal tubules. They raise the levels of renin, angiotensin I and II, and aldosterone via inhibition of negative feedback.

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Educational objective:
Beta-adrenergic blocking drugs inhibit renin release by blocking beta-1 receptor-mediated regulation of the renin-angiotensin-aldosterone system. This reduces plasma renin activity, with a resulting reduction in angiotensin I, angiotensin II, and aldosterone levels.

References

- Beta-adrenergic receptor blockade as a therapeutic approach for suppressing the renin-angiotensin-

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A 58-year-old man comes to the office due to urinary symptoms. Over the past year, he has had difficulty initiating urination and a weakened urine stream. He also has frequent nocturnal voiding. The patient has not passed any visible blood clots and has had no dysuria, fever, recent illnesses, or urinary trauma. He has no other medical conditions and takes no medications. Vital signs are within normal limits. Rectal examination reveals a smooth, enlarged prostate with no tenderness to palpation. Prostate-specific antigen is within the normal range. Urinalysis reveals 20-30 red blood cells per high power field and no urinary casts. Cystoscopy is performed and shows increased bladder wall trabeculations with normal appearing mucosa. Which of the following is the most likely cause of this patient's hematuria?

- A. Acquired bleeding disorder
- B. Friable prostatic blood vessels
- C. Glomerulonephritis
- D. Interstitial cystitis
- E. Transitional cell carcinoma of bladder

Submit

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A 58-year-old man comes to the office due to urinary symptoms. Over the past year, he has had difficulty initiating urination and a weakened urine stream. He also has frequent nocturnal voiding. The patient has not passed any visible blood clots and has had no dysuria, fever, recent illnesses, or urinary trauma. He has no other medical conditions and takes no medications. Vital signs are within normal limits. Rectal examination reveals a smooth, enlarged prostate with no tenderness to palpation. Prostate-specific antigen is within the normal range. Urinalysis reveals 20-30 red blood cells per high power field and no urinary casts. Cystoscopy is performed and shows increased bladder wall trabeculations with normal appearing mucosa. Which of the following is the most likely cause of this patient's hematuria?

- ✗ A. Acquired bleeding disorder (0%)
- ✓ B. Friable prostatic blood vessels (42%)
- C. Glomerulonephritis (3%)
- D. Interstitial cystitis (24%)
- E. Transitional cell carcinoma of bladder (28%)

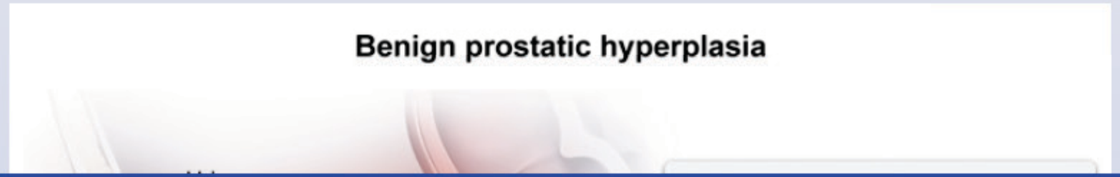
Incorrect
Correct answer
B

42%
Answered correctly

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Time Spent

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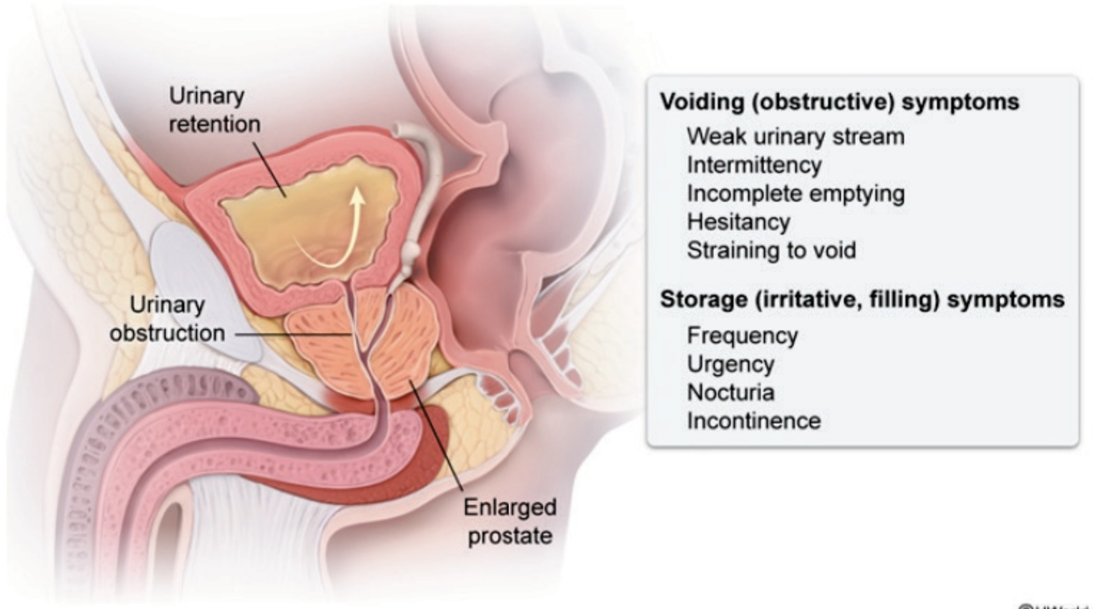
Explanation



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B

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This
pros
BPH
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The
specific antigen (**PSA**) can be **normal or elevated** in BPH, so it is not useful for BPH diagnosis (it is more useful
for prostate cancer screening)

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This patient's urinary hesitancy, weakened urinary stream, and nocturia in the setting of an enlarged, nontender prostate raises strong suspicion for **benign prostatic hyperplasia** (BPH), a common condition in men age >50. In BPH, stromal and glandular hyperplasia in the periurethral and transitional zone can impinge the urethra, leading to progressive urinary voiding (eg, hesitancy, weakened stream) and storage (eg, nocturia, frequency) symptoms. The diagnosis is generally confirmed when examination reveals a smooth, **large, non-tender prostate**. Prostate-specific antigen (**PSA**) can be **normal or elevated** in BPH, so it is not useful for BPH diagnosis (it is more useful for prostate cancer screening).

Microscopic or gross hematuria can sometimes arise in patients with BPH due to the formation of new, **friable blood vessels** in the area of prostatic hyperplasia. Further examination with cystoscopy is generally warranted to rule out other (potentially life-threatening) causes of hematuria such as bladder cancer and urinary calculi. Cystoscopy in those with BPH often shows **increased detrusor wall trabeculations** due to detrusor muscle hypertrophy (to generate increased pressure to overcome urethral obstruction).

(Choice A) Hematuria is typically caused by urinary tract pathology rather than a systemic bleeding disorder. Furthermore, systemic bleeding disorders are often associated with other sites of mucosal bleeding (eg, nosebleed) or bruising. The presence of lower urinary tract symptoms and prostatic enlargement make BPH more likely.

(Choice C) Glomerulonephritis can cause hematuria but is also associated with red blood cell casts. The urine is often described as dark, and the onset is generally more acute (eg, following an upper respiratory infection).

(Choice D) Although interstitial cystitis can cause urinary frequency, urgency, and nocturia, it is more common in women and usually presents with suprapubic pain (often worse with bladder filling and better with voiding). In addition, hematuria is uncommon, and cystoscopy is likely to show patchy erythema and petechiae.

(Choice E) Bladder cancer often presents with painless hematuria and storage symptoms (eg, frequency, urgency). However, voiding symptoms (eg, hesitancy, decreased force of stream) are less common, and most cases arise in the setting of advanced age, smoking, or chemical/carcinogen exposures in the workplace.

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for prostate cancer screening).

Microscopic or gross hematuria can sometimes arise in patients with BPH due to the formation of new, **friable blood vessels** in the area of prostatic hyperplasia. Further examination with cystoscopy is generally warranted to rule out other (potentially life-threatening) causes of hematuria such as bladder cancer and urinary calculi. Cystoscopy in those with BPH often shows **increased detrusor wall trabeculations** due to detrusor muscle hypertrophy (to generate increased pressure to overcome urethral obstruction).

(Choice A) Hematuria is typically caused by urinary tract pathology rather than a systemic bleeding disorder. Furthermore, systemic bleeding disorders are often associated with other sites of mucosal bleeding (eg, nosebleed) or bruising. The presence of lower urinary tract symptoms and prostatic enlargement make BPH more likely.

(Choice C) Glomerulonephritis can cause hematuria but is also associated with red blood cell casts. The urine is often described as dark, and the onset is generally more acute (eg, following an upper respiratory infection).

(Choice D) Although interstitial cystitis can cause urinary frequency, urgency, and nocturia, it is more common in women and usually presents with suprapubic pain (often worse with bladder filling and better with voiding). In addition, hematuria is uncommon, and cystoscopy is likely to show patchy erythema and petechiae.

(Choice E) Bladder cancer often presents with painless hematuria and storage symptoms (eg, frequency, urgency). However, voiding symptoms (eg, hesitancy, decreased force of stream) are less common, and most cases arise in the setting of advanced age, smoking, or chemical/carcinogen exposures in the workplace. Cystoscopy generally reveals a mucosal mass, not increased trabeculations.

Educational objective:
Benign prostatic hyperplasia (BPH) is associated with stromal and glandular growth in the periurethral and transitional zone of the prostate. The hyperplastic cells are supported by the formation of new blood vessels, which may be friable. Therefore, BPH is often associated with microscopic or gross hematuria.

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A 72-year-old woman is evaluated due to a month of fatigue and shortness of breath on exertion. The patient has also had lower back pain but no fever or cough. She takes valsartan for hypertension. Temperature is 37.2 C (99 F), blood pressure is 130/80 mm Hg, pulse is 84/min, and respirations are 14/min. On physical examination, the conjunctivae are pale. The remainder of the examination is normal. Laboratory results are as follows:

Hemoglobin	8.2 g/dL
Creatinine	2.1 mg/dL
Calcium	11.2 mg/dL
Total protein	8.5 g/dL
Albumin	3.7 g/dL

X-rays of the lower back demonstrate multiple areas of radiolucency in the L4 and L5 vertebrae. Serum protein electrophoresis reveals a monoclonal gamma globulin spike. Further studies are most likely to show which of the following?

	Parathyroid hormone (PTH)	Urinary calcium	1,25-dihydroxyvitamin D	PTH-related protein
A.	Decreased	Decreased	Normal	Normal
B.	Decreased	Increased	Increased	Normal
C.	Decreased	Increased	Normal	Increased
D.	Decreased	Increased	Decreased	Normal
E.	Increased	Increased	Increased	Normal

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F), blood pressure is 130/80 mm Hg, pulse is 84/min, and respirations are 14/min. On physical examination, the conjunctivae are pale. The remainder of the examination is normal. Laboratory results are as follows:

Hemoglobin	8.2 g/dL
Creatinine	2.1 mg/dL
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A.	Decreased	Decreased	Normal	Normal
B.	Decreased	Increased	Increased	Normal
C.	Decreased	Increased	Normal	Increased
D.	Decreased	Increased	Decreased	Normal
E.	Increased	Increased	Increased	Normal
F.	Increased	Decreased	Normal	Normal

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Hemoglobin	8.2 g/dL
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Calcium	11.2 mg/dL
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X-rays of the lower back demonstrate multiple areas of radiolucency in the L4 and L5 vertebrae. Serum protein electrophoresis reveals a monoclonal gamma globulin spike. Further studies are most likely to show which of the following?

		Parathyroid hormone (PTH)	Urinary calcium	1,25-dihydroxyvitamin D	PTH-related protein	
✗	A.	Decreased	Decreased	Normal	Normal	(5%)
	B.	Decreased	Increased	Increased	Normal	(9%)
	C.	Decreased	Increased	Normal	Increased	(18%)
✓	D.	Decreased	Increased	Decreased	Normal	(51%)
	E.	Increased	Increased	Increased	Normal	(7%)
	F.	Increased	Decreased	Normal	Normal	(7%)

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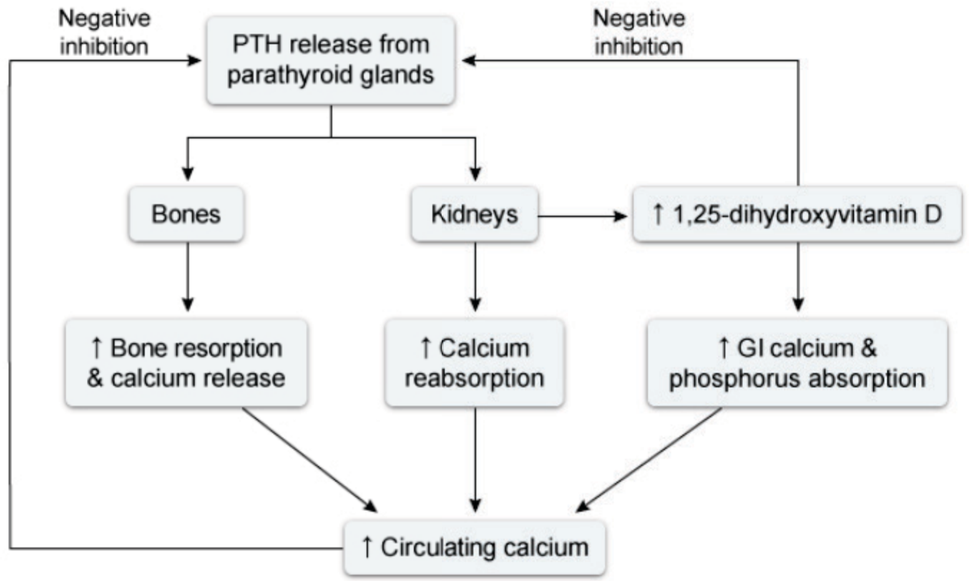
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Parathyroid hormone, vitamin D & calcium axis



GI = gastrointestinal; **PTH** = parathyroid hormone.

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- **Low 1,25 dihydroxyvitamin D levels** – low PTH (and renal insufficiency) reduce the activity of renal 1-alpha-

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Multiple myeloma (MM) is a plasma cell malignancy that generates monoclonal immunoglobulin. It is classically characterized by anemia, bone pain/radiolucent lesions, and **hypercalcemia** due to tumor infiltration of the bone marrow; renal insufficiency can also occur due to hypercalcemia and clogging of the renal tubules with immunoglobulin light chains.

MM tumor cells secrete potent **osteolytic cytokines** (eg, tumor necrosis factor-alpha) that liberate calcium from bone and result in hypercalcemia. Elevated serum calcium inhibits the release of parathyroid hormone (PTH) from parathyroid cells, which has several downstream effects including:

- **Hypercalciuria** – low PTH levels increase urinary calcium excretion due to reduced calcium reabsorption in the distal tubules and collecting ducts of the kidney (where PTH exerts its effects)
- **Low 1,25 dihydroxyvitamin D levels** – low PTH (and renal insufficiency) reduce the activity of renal 1-alpha-hydroxylase, the enzyme that converts 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (the more active form)

Therefore, patients with MM classically have low PTH and 1,25-dihydroxyvitamin D levels and elevated urinary calcium.

(Choice A) Thiazide diuretics cause hypercalcemia by promoting calcium reabsorption in the distal convoluted tubule. This leads to reduced urinary calcium excretion and low serum PTH levels (elevated serum calcium reduces PTH release). Angiotensin receptor blockers (eg, valsartan) do not increase renal calcium reabsorption.

(Choice B) Granulomatous diseases (eg, sarcoidosis, tuberculosis) can cause hypercalcemia due to production of 1,25-dihydroxyvitamin D by 1-alpha-hydroxylase in granulomatous tissue. This increases the intestinal absorption and urinary excretion of calcium (the latter effect being caused by concomitant suppression of PTH).

(Choice C) Production of PTH-related protein (PTHrP) is the most common cause of hypercalcemia in malignancy (eg, squamous cell carcinoma). PTHrP increases osteoclast activity and renal calcium absorption with minimal effect on 1,25-dihydroxyvitamin D. The hypercalcemia seen in MM is not typically due to PTHrP; it is caused by osteolytic cytokines.

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(Choice A) Thiazide diuretics cause hypercalcemia by promoting calcium reabsorption in the distal convoluted tubule. This leads to reduced urinary calcium excretion and low serum PTH levels (elevated serum calcium reduces PTH release). Angiotensin receptor blockers (eg, valsartan) do not increase renal calcium reabsorption.

(Choice B) Granulomatous diseases (eg, sarcoidosis, tuberculosis) can cause hypercalcemia due to production of 1,25-dihydroxyvitamin D by 1-alpha-hydroxylase in granulomatous tissue. This increases the intestinal absorption and urinary excretion of calcium (the latter effect being caused by concomitant suppression of PTH).

(Choice C) Production of PTH-related protein (PTHrP) is the most common cause of hypercalcemia in malignancy (eg, squamous cell carcinoma). PTHrP increases osteoclast activity and renal calcium absorption with minimal effect on 1,25-dihydroxyvitamin D. The hypercalcemia seen in MM is not typically due to PTHrP; it is caused by osteolytic cytokines.

(Choice E) Primary hyperparathyroidism is characterized by excessive PTH release, leading to increased bone resorption and 1,25-dihydroxyvitamin D formation. Urinary calcium excretion is elevated due to the increased filtered calcium load (despite the increased renal reabsorption induced by PTH).

(Choice F) Familial hypocalciuric hypercalcemia is caused by inactivating mutations of the Ca^{2+}-sensing receptor in the nephron and parathyroid glands. Renal calcium reabsorption is increased (urinary calcium excretion is low) and higher serum calcium levels are required to suppress PTH release (serum PTH is slightly elevated or inappropriately normal).

Educational objective:
Multiple myeloma is associated with increased bone resorption due to the production of tumor-related cytokines. This results in elevated serum calcium levels, which reduce parathyroid hormone (PTH) production. Low PTH decreases renal calcium reabsorption (hypercalciuria), and, in combination with renal insufficiency, reduces 1,25-dihydroxyvitamin D synthesis.

References

- Multiple myeloma: from diagnosis to treatment.

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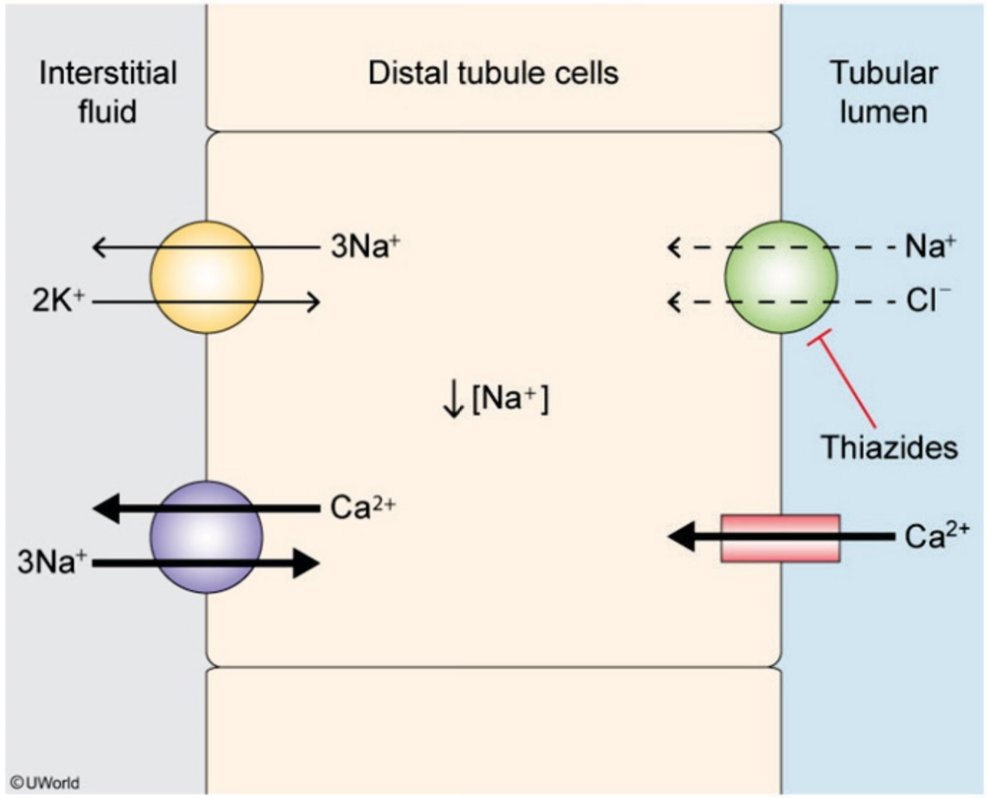
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filtered calcium load (despite the increased renal reabsorption induced by PTH).

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Effect of thiazide diuretics on distal tubular calcium reabsorption



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A 4-week-old, full-term boy is brought to the emergency department due to vomiting. His parents describe the emesis as undigested formula without blood or bile. The vomiting occurs after feeds and has increased in frequency and force over the past 3 days. He is afebrile. Blood pressure is normal, pulse is 182/min, and oxygen saturation of 98% on room air. Examination shows a sunken anterior fontanelle and dry mucous membranes. Cardiac examination reveals tachycardia but no murmurs or gallops. The abdomen is soft, nontender, and nondistended. Arterial blood gas analysis is most likely to reveal which of the following sets of values?

	pH	$PaCO_2$	HCO_3^-	Anion gap
○ A.	7.29	30	14	Elevated
○ B.	7.30	55	26	Normal
○ C.	7.41	39	24	Normal
○ D.	7.49	46	34	Normal
○ E.	7.53	45	36	Elevated

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	pH	$PaCO_2$	HCO_3^-	Anion gap	
A.	7.29	30	14	Elevated	(6%)
✗ B.	7.30	55	26	Normal	(3%)
C.	7.41	39	24	Normal	(7%)
✓ D.	7.49	46	34	Normal	(71%)
E.	7.53	45	36	Elevated	(11%)

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71%
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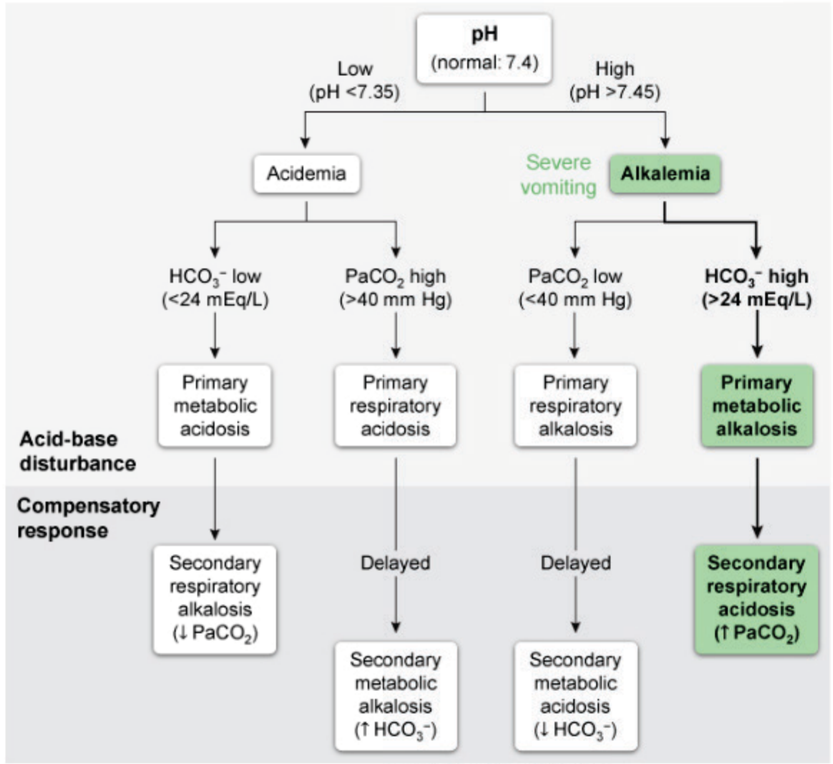
Arterial blood gas interpretation of acid-base disorders

	Low	pH (normal: 7.4)	High

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Arterial blood gas interpretation of acid-base disorders



* The normal ranges for $PaCO_2$ and HCO_3^- vary slightly around 40 mm Hg and 24 mEq/L.
For simplicity, these numbers should be used as a normal baseline for acid-base calculations.

HCO_3^- = bicarbonate; **$PaCO_2$** = partial pressure of carbon dioxide in arterial blood.

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This 4-week-old infant has had severe, nonbilious **vomiting** (suggesting pyloric stenosis) and now has multiple signs of **volume depletion** (eg, dry mucous membranes, sunken anterior fontanelle, tachycardia). **Primary metabolic alkalosis** (elevated pH >7.45, elevated HCO_3^- >24 mEq/L) with respiratory compensation ($PaCO_2$ >40 mm Hg) is the expected acid-base disturbance in such a setting.

With vomiting, there is loss of hydrochloric acid (H^+ and Cl^-) and fluid volume from the stomach. This causes metabolic alkalosis through multiple mechanisms:

- The **loss of H^+ ions** reduces the amount of carbonic acid (H_2CO_3) buffer in the body and increases the relative quantity of HCO_3^-.
- Volume loss and reduced oral intake lead to intravascular volume depletion and decreased renal perfusion, triggering activation of the renin-angiotensin-aldosterone system. Aldosterone stimulates Na^+ reabsorption in the distal tubules at the expense of **increased renal H^+ and K^+ excretion**.
- Hypovolemia, hypokalemia, and hypochloremia (from loss of hydrochloric acid) all contribute to impaired renal HCO_3^- excretion, leading to **increased renal HCO_3^- reabsorption**.
- Hypokalemia also causes cells to **exchange intracellular K^+ for extracellular H^+**, which increases serum potassium at the expense of decreased H^+ concentration (**increased blood alkalinity**).

Treatment of the underlying cause of vomiting and restoration of fluid volume with normal saline (typically with potassium repletion) is needed to resolve the hypokalemic, hypochloremic metabolic alkalosis.

(Choice A) Low pH and low HCO_3^- indicate metabolic acidosis, which can have a normal (eg, due to diarrhea or renal tubular acidosis) or elevated anion gap. $PaCO_2$ is low due to respiratory compensation.

(Choice B) Low pH and elevated $PaCO_2$ indicate respiratory acidosis. The near-normal HCO_3^- is consistent with minimal metabolic compensation, suggesting the respiratory acidosis is acute (eg, due to hypoventilation from opioid overdose).

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- Hypovolemia, hypokalemia, and hypochloremia (from loss of hydrochloric acid) all contribute to impaired renal HCO_3^- excretion, leading to **increased renal HCO_3^- reabsorption**.
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(Choice B) Low pH and elevated $PaCO_2$ indicate respiratory acidosis. The near-normal HCO_3^- is consistent with minimal metabolic compensation, suggesting the respiratory acidosis is acute (eg, due to hypoventilation from opioid overdose).

(Choice C) These acid-base values are considered normal, indicating an absence of acid-base disturbance.

(Choice E) High pH and elevated HCO_3^- indicate metabolic alkalosis, with elevated $PaCO_2$ indicating respiratory compensation (as expected in this patient). A small increase in the anion gap may be seen with metabolic alkalosis due to a buffering effect involving the release of H^+ from albumin, which increases albumin's anionic charge. However, a clinically significant elevation in the anion gap is mostly a characteristic of some types of metabolic *acidosis*.

Educational objective:
Severe vomiting leads to metabolic alkalosis through multiple mechanisms, including loss of H^+ from the gastrointestinal tract, volume and Cl^- depletion that induces renal retention of HCO_3^-, and hypokalemia-induced intracellular shifting of H^+.

References

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Compensatory response

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Appropriate compensatory $PaCO_2$ or HCO_3^- changes in acid-base disorders	
Metabolic acidosis (acute or chronic)	Expected $PaCO_2 = (1.5 \times HCO_3^-) + 8 \pm 2$ (Winters formula)
Metabolic alkalosis (acute or chronic)	~7 mm Hg ↑ in $PaCO_2$ per 10 mEq/L ↑ in HCO_3^-
Respiratory acidosis (chronic only*)	~4 mEq/L ↑ in HCO_3^- per 10 mm Hg ↑ in $PaCO_2$
Respiratory alkalosis (chronic only*)	~4 mEq/L ↓ in HCO_3^- per 10 mm Hg ↓ in $PaCO_2$
*Compensation for respiratory disturbances is minimal in the acute setting. The full level of chronic compensation is achieved after ~72 hr. For simplicity, normal baseline $PaCO_2$ & HCO_3^- should be considered 40 mm Hg & 24 mEq/L, respectively.	

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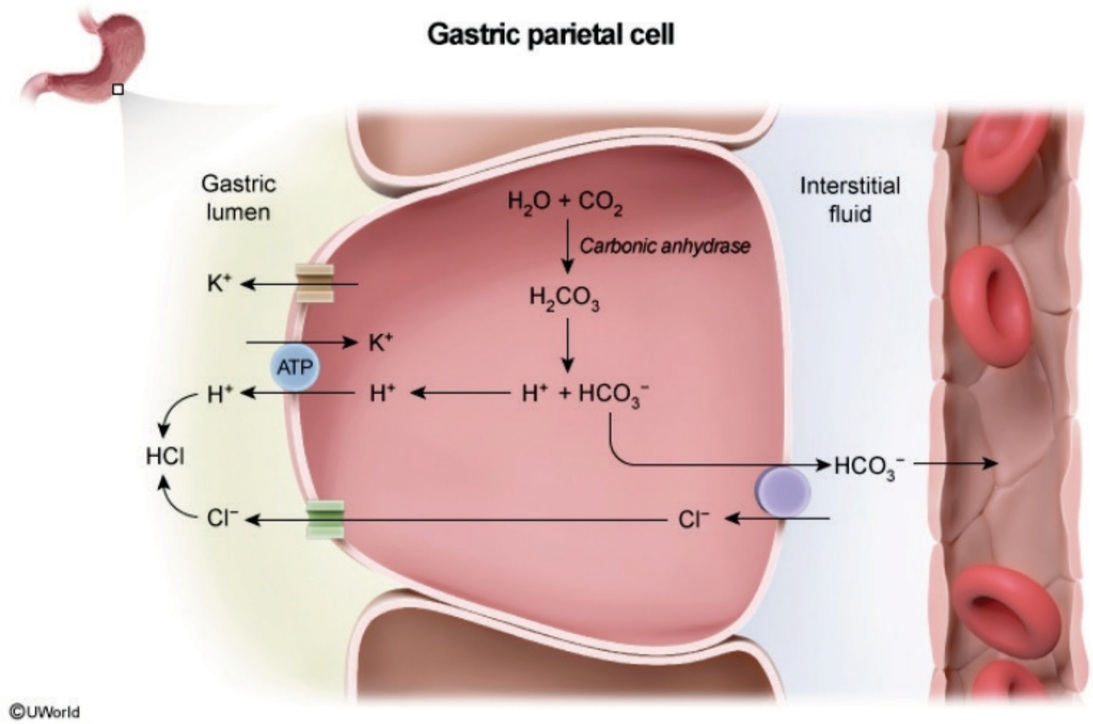
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- Hypokalemia also causes cells to **exchange intracellular K^+ for extracellular H^+**, which increases serum

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Compensatory response

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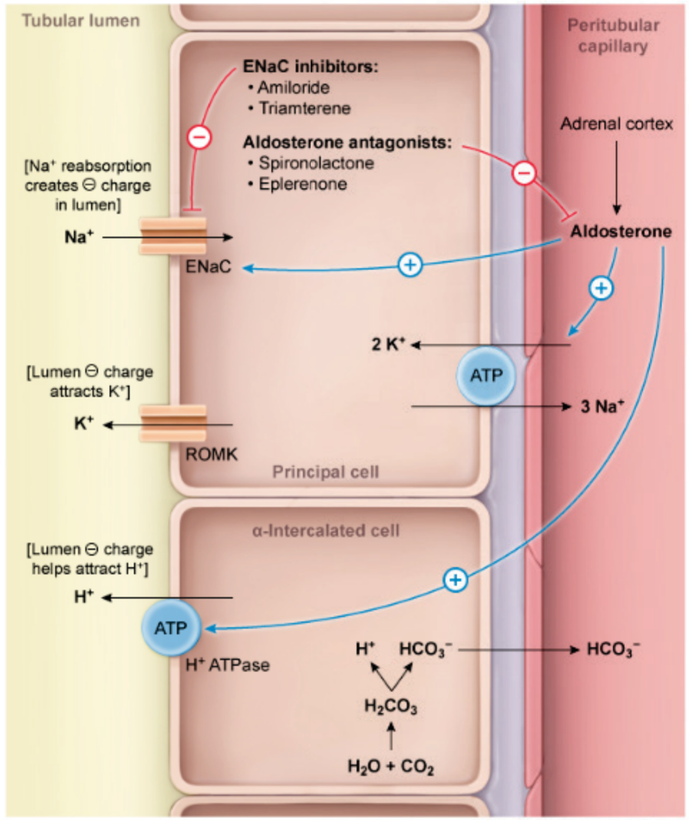
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- Hypokalemia also causes cells to **exchange intracellular K^+ for extracellular H^+**, which increases serum

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Action of aldosterone in the collecting duct of the nephron



ENaC = epithelial sodium channel; **ROMK** = renal outer medullary potassium channel. ©UWorld

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mm Hg) is the expected acid-base disturbance in such a setting.

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(Choice E) High pH and elevated HCO_3^- indicate metabolic alkalosis, with elevated $PaCO_2$ indicating respiratory

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Anion gap metabolic acidosis	
Calculation	Anion gap = sodium – (chloride + bicarbonate) (normal: 10-14 mEq/L)
Common causes Mnemonic: MUDPILES	• Methanol • Uremia • Diabetic ketoacidosis • Propylene glycol/paraldehyde • Isoniazid/iron • Lactic acidosis • Ethylene glycol (antifreeze) • Salicylate (aspirin)

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A 7-year-old boy is brought to the clinic for follow-up care. The patient recently completed a course of antibiotics for a urinary tract infection caused by *Escherichia coli*. He has had 2 febrile urinary tract infections in the past, both of which resolved following antibiotic therapy. Vital signs are normal. Examination of the abdomen is unremarkable. Renal ultrasound examination reveals no signs of hydronephrosis. Voiding cystourethrogram shows contrast filling the bladder and extending linearly toward the umbilicus. This patient most likely has a congenital abnormality related to which of the following structures?

- A. Omphalomesenteric duct
- B. Umbilical artery
- C. Umbilical vein
- D. Urachus
- E. Ureter
- F. Urorectal septum

Submit

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- A. Omphalomesenteric duct (6%)
- B. Umbilical artery (0%)
- ✗ C. Umbilical vein (1%)
- ✓ D. Urachus (84%)
- E. Ureter (5%)
- F. Urorectal septum (0%)

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84%
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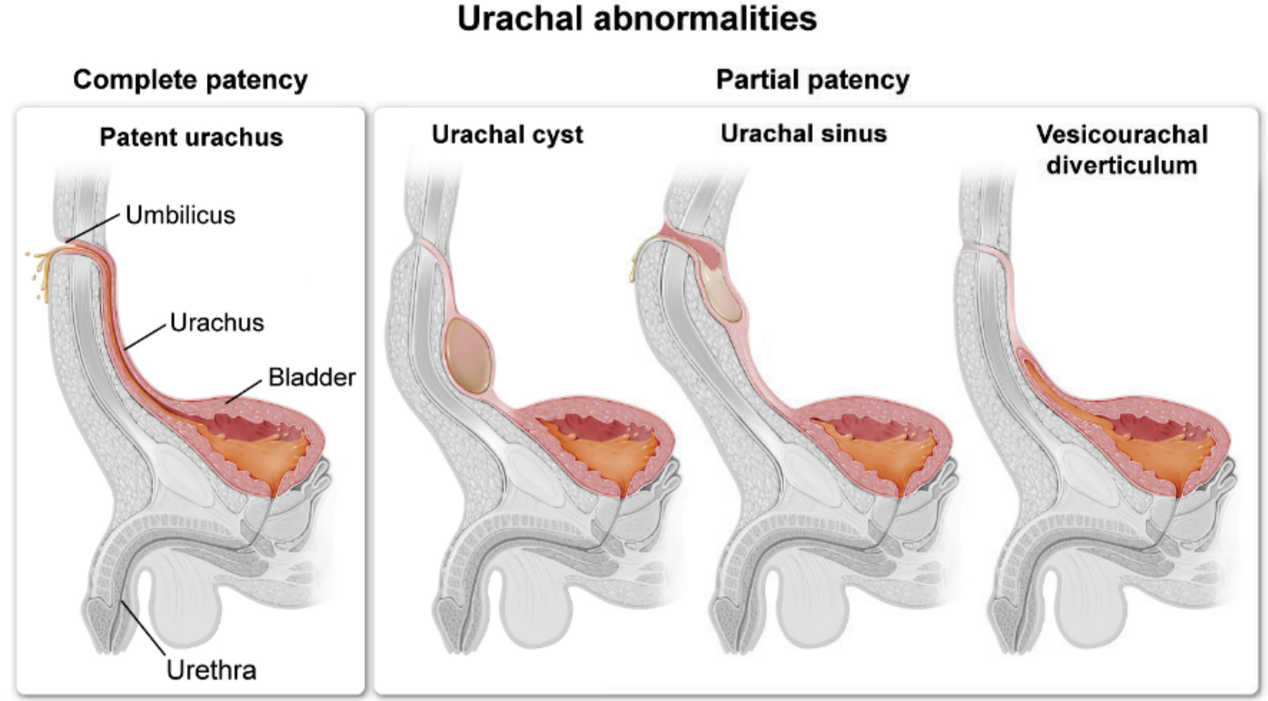
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B. Umbilical artery (0%)

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This patient's imaging findings are consistent with a congenital urachal anomaly. In utero, the caudal yolk sac forms a tubular outpouching called the allantois, which extends from the embryologic bladder to the umbilicus. As the **bladder descends** into the fetal pelvis, it **stretches the allantois**, which becomes thin and narrow. Normally, epithelial proliferation obliterates the lumen of the allantois by 12 weeks gestation, forming a **fibrous cord** known as the **urachus**.

Failed or inadequate epithelial proliferation leads to a complete or partial patent urachus:

- Complete patent urachus: Neonates usually have urinary umbilical drainage on presentation due to a continuous connection from the bladder to the umbilicus.
- Partial patent urachus**:** A range of defects may occur depending on the location of the patency, including a urachus that is open only to the umbilicus (urachal sinus), to the bladder (urachal diverticulum), or centrally (urachal cyst).

This patient with a normal abdominal examination most likely has a **urachal diverticulum**, as seen on imaging as a linear extension of urine from the bladder toward the umbilicus. **Urinary stasis** within the diverticulum is a risk factor for recurrent **urinary tract infection**, as seen in this case.

(Choice A) Similar to the allantois, the omphalomesenteric (or vitelline) duct is a tubular outpouching of the yolk sac that involutes in early gestation. However, because it connects the yolk sac to the fetal midgut, failed obliteration results in a connection between umbilicus and bowel (not bladder).

(Choices B and C) The umbilical arteries and vein are contained within the umbilical cord, and abnormalities (eg, single umbilical artery) are usually isolated. These vascular structures are not connected to the bladder lumen.

(Choice E) The ureters are derived from the mesonephric duct, and abnormalities may result in ectopic ureteral insertion along the mesonephric system (eg, urethra). A midline bladder diverticulum directed toward the umbilicus would not be expected.

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(Choice F) The urorectal septum divides the cloaca into the distal anorectal and urogenital regions. Developmental abnormalities would not explain this patient's abnormal urinary flow from the bladder to the umbilicus.

Educational objective:
Congenital anomalies of the urachus result in an abnormal connection between the bladder and the umbilicus. Full patency results in urinary umbilical leakage, whereas partial patency can result in a range of defects, including a bladder diverticulum (increases the risk of urinary tract infection due to stasis of urine).

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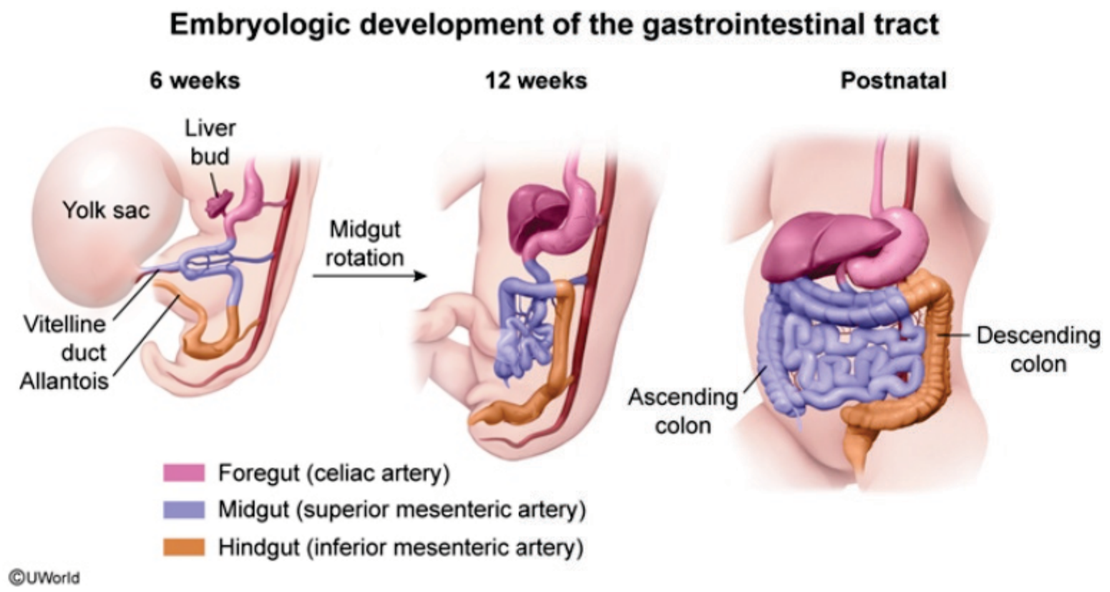
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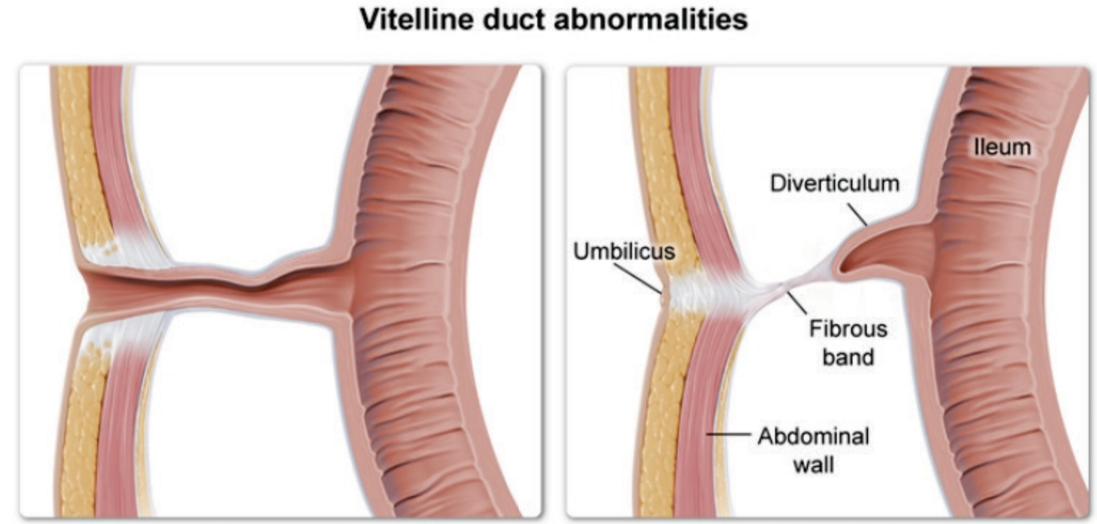
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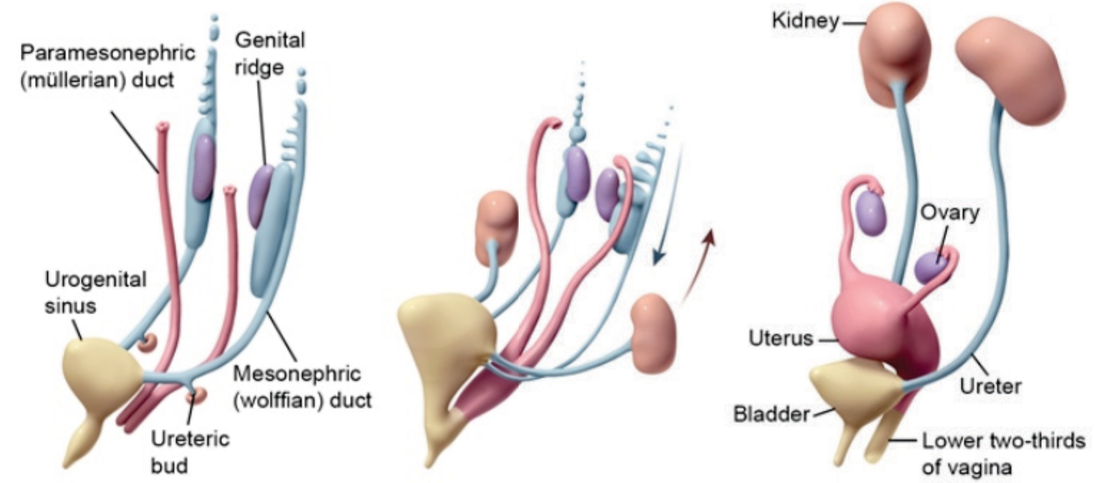
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Educational objective:

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Urogenital development



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A 64-year-old man comes to the hospital due to generalized weakness and fatigue for the past several weeks. He has a history of uncontrolled hypertension and nonadherence to medical therapy. Blood pressure is 160/100 mm Hg, pulse is 90/min, and respirations are 22/min. Oxygen saturation is 95% on room air. Physical examination shows elevated jugular venous pressure, bilateral crackles, and 3+ pitting edema in both legs. Laboratory results are as follows:

Blood urea nitrogen	82 mg/dL
Creatinine	4.8 mg/dL

Which of the following additional findings are most likely present in this patient?

	pH	Bicarbonate (mEq/L)	$PaCO_2$ (mm Hg)	Anion gap (mEq/L)
○ A.	7.15	16	48	18
○ B.	7.25	12	28	20
○ C.	7.31	18	37	12
○ D.	7.32	25	50	10
○ E.	7.39	23	39	12

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Which of the following additional findings are most likely present in this patient?

		pH	Bicarbonate (mEq/L)	$PaCO_2$ (mm Hg)	Anion gap (mEq/L)	
✗	A.	7.15	16	48	18	(7%)
✓	B.	7.25	12	28	20	(49%)
	C.	7.31	18	37	12	(22%)
	D.	7.32	25	50	10	(11%)
	E.	7.39	23	39	12	(9%)

Incorrect
Correct answer
B

49%
Answered correctly

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Time Spent

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Explanation

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Explanation

Metabolic acidosis		
Type	**Normal anion gap**	**Elevated anion gap**
Mechanism	• Loss of bicarbonate	• Accumulation of unmeasured acidic compounds
Common causes	• Severe diarrhea • Renal tubular acidosis • Excessive saline infusion	• Lactic acidosis • Diabetic ketoacidosis • Renal failure (uremia) • Methanol, ethylene glycol • Salicylate toxicity

This patient's markedly elevated blood urea nitrogen (BUN) and serum creatinine in the setting of uncontrolled hypertension suggest advanced **chronic kidney disease** (CKD), a condition commonly presenting with fatigue, generalized weakness, and evidence of volume overload (eg, jugular venous distension, peripheral edema). Once CKD becomes advanced (eg, serum creatinine >3 mg/dL), **anion gap metabolic acidosis** with **respiratory compensation** is expected.

CKD involves a gradual decline in glomerular filtration rate (GFR), as evidenced by a slow increase in serum creatinine. Urea, which is formed in the liver from ammonia and other nitrogenous wastes derived from protein breakdown, is normally cleared by the kidneys and also accumulates as GFR declines. With advanced CKD, BUN levels become markedly elevated (eg, >60 mg/dL). Although urea is uncharged and does not contribute to acidemia or an elevation in the anion gap, elevated BUN (ie, **uremia**) is a marker for the reduced renal clearance and consequent **accumulation of unmeasured acidic compounds** (eg, hydrogen phosphate, hydrogen sulfate, uric acid). These compounds donate hydrogen ions (H^+) to bind up bicarbonate (HCO_3^-) and acidify the blood, and

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In response to the metabolic acidosis, the lungs compensate with hyperventilation to **decrease $PaCO_2$** and help normalize pH.

(Choice A) Low pH with low HCO_3^- and elevated $PaCO_2$ represents mixed metabolic and respiratory acidosis. Such a scenario with an elevated anion gap may be seen with sepsis (ie, lactic acidosis) with acute respiratory failure.

(Choice C) Low pH with low HCO_3^- and slightly reduced $PaCO_2$ represents metabolic acidosis with respiratory compensation. A normal anion gap is expected with metabolic acidosis that results from loss of HCO_3^- (eg, severe diarrhea). However, this patient with CKD will have accumulation of unmeasured acidic compounds, resulting in an elevated anion gap.

(Choice D) Low pH with elevated $PaCO_2$ indicates respiratory acidosis. Minimal increase in HCO_3^- suggests acute

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levels become markedly elevated (eg, >60 mg/dL). Although urea is uncharged and does not contribute to acidemia or an elevation in the anion gap, elevated BUN (ie, **uremia**) is a marker for the reduced renal clearance and consequent **accumulation of unmeasured acidic compounds** (eg, hydrogen phosphate, hydrogen sulfate, uric acid). These compounds donate hydrogen ions (H^+) to bind up bicarbonate (HCO_3^-) and acidify the blood, and the remaining anionic component **increases the anion gap** (normal: 10-14 mEq/L).

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(Choice D) Low pH with elevated $PaCO_2$ indicates respiratory acidosis. Minimal increase in HCO_3^- suggests acute respiratory acidosis (eg, acute opioid overdose) as there has not been time for metabolic compensation to occur (full metabolic compensation requires approximately 72 hours).

(Choice E) These acid-base and anion gap findings are within normal limits and indicate an absence of acid-base disturbance.

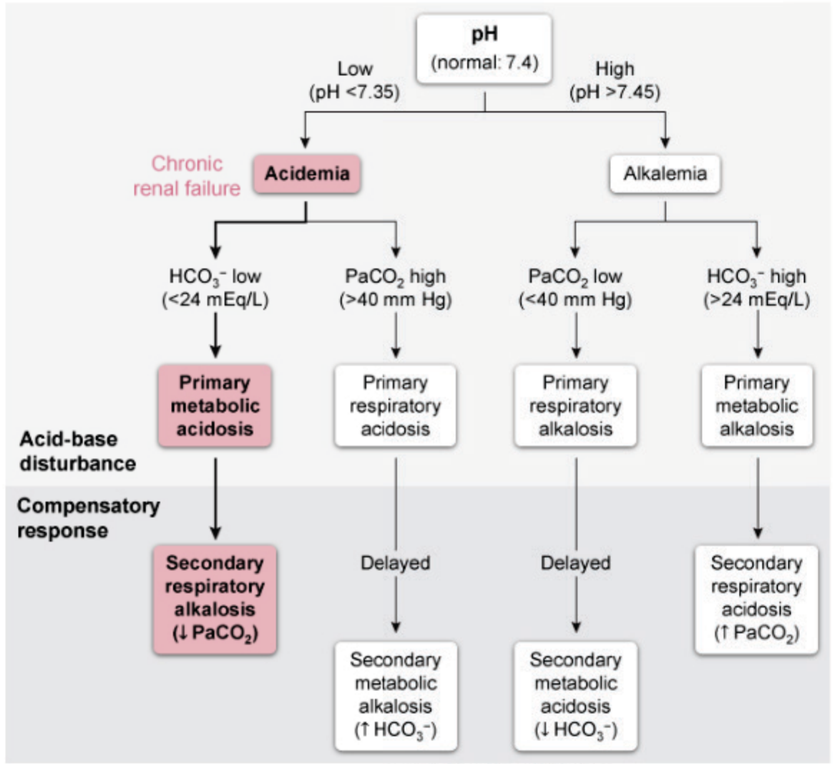
Educational objective:
Advanced chronic kidney disease typically involves the accumulation of unmeasured acidic compounds in the blood; therefore, anion gap metabolic acidosis with respiratory compensation is expected.

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Mechanism	• Loss of bicarbonate	compounds

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Arterial blood gas interpretation of acid-base disorders



* The normal ranges for $PaCO_2$ and HCO_3^- vary slightly around 40 mm Hg and 24 mEq/L.
For simplicity, these numbers should be used as a normal baseline for acid-base calculations.

HCO_3^- = bicarbonate; **$PaCO_2$** = partial pressure of carbon dioxide in arterial blood.

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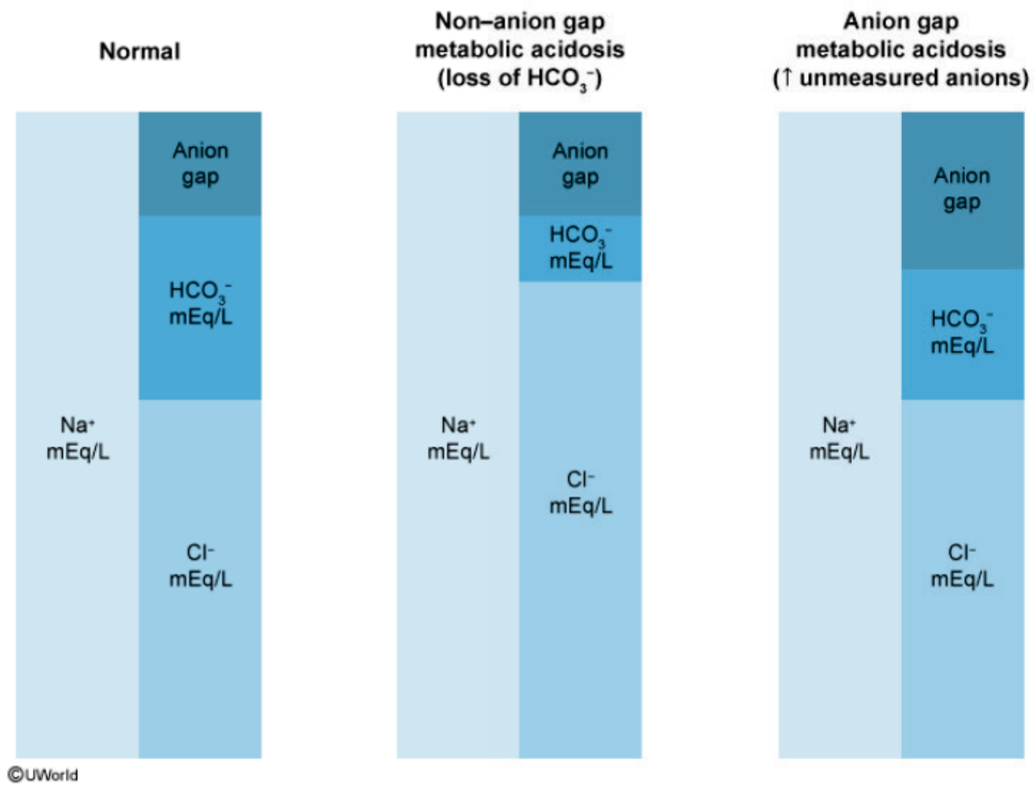
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Such a scenario with an elevated anion gap may be seen with sepsis (ie, lactic acidosis) with acute respiratory failure.

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Mechanism	• Loss of bicarbonate	compounds

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Such a scenario with an elevated anion gap may be seen with sepsis (ie, lactic acidosis) with acute respiratory failure.

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Common	• Renal tubular acidosis • Renal failure (uremia)

Exhibit Display

Appropriate compensatory $PaCO_2$ or HCO_3^- changes in acid-base disorders

Metabolic acidosis (acute or chronic)	Expected $PaCO_2 = (1.5 \times HCO_3^-) + 8 \pm 2$ (Winters formula)
Metabolic alkalosis (acute or chronic)	~7 mm Hg ↑ in $PaCO_2$ per 10 mEq/L ↑ in HCO_3^-
Respiratory acidosis (chronic only*)	~4 mEq/L ↑ in HCO_3^- per 10 mm Hg ↑ in $PaCO_2$
Respiratory alkalosis (chronic only*)	~4 mEq/L ↓ in HCO_3^- per 10 mm Hg ↓ in $PaCO_2$

*Compensation for respiratory disturbances is minimal in the acute setting. The full level of chronic compensation is achieved after ~72 hr. For simplicity, normal baseline $PaCO_2$ & HCO_3^- should be considered 40 mm Hg & 24 mEq/L, respectively.

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compensation. A normal anion gap is expected with metabolic acidosis that results from loss of HCO_3^- (eg, severe

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A 27-year-old nursing assistant with a history of major depression and bulimia is brought to the emergency department after a suicide attempt. She claims to have ingested several diuretic pills 18 hours ago. The patient complains of frequent, large-volume urinations that started shortly after she ingested the pills. She has also been very thirsty but she denies nausea, vomiting, or diarrhea. Her temperature is 36.7 C (98 F), blood pressure is 96/60 mm Hg, pulse is 110/min, and respirations are 14/min. Physical examination shows dry oral mucosa and reduced skin turgor. Laboratory results are as follows:

Serum chemistry	
Sodium	122 mEq/L
Potassium	2.8 mEq/L
Chloride	84 mEq/L
Bicarbonate	28 mEq/L
Blood urea nitrogen	22 mg/dL
Creatinine	1.4 mg/dL
Calcium	11.4 mg/dL
Albumin	3.9 g/dL

Which of the following medications did this patient most likely ingest?

- A. Acetazolamide
- B. Amiloride
- C. Hydrochlorothiazide
- D. Spironolactone

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- E. Torsemide

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Albumin	3.9 g/dL

Which of the following medications did this patient most likely ingest?

- A. Acetazolamide (3%)
- ✗ B. Amiloride (1%)
- ✓ C. Hydrochlorothiazide (78%)
- D. Spironolactone (2%)
- E. Torsemide (13%)

Incorrect
Correct answer
C

78%
Answered correctly

35 secs
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Diuretic effects			
Drug	**Mechanism of action**	**Electrolyte abnormalities**	**Clinical indications**
Loop diuretics • Furosemide • Torsemide • Bumetanide • Ethacrynic acid	• Inhibits the Na-K-2Cl cotransporter in the thick ascending limb of loop of Henle	• Hypokalemia • Metabolic alkalosis • Hypocalcemia	• Volume-overloaded states (eg, congestive heart failure)
Thiazide diuretics • Hydrochlorothiazide • Chlorthalidone • Indapamide • Metolazone	• Inhibits the Na-Cl cotransporter in the early distal convoluted tubule	• Hyponatremia • Hypokalemia • Metabolic alkalosis • Hypercalcemia	• Hypertension • Calcium nephrolithiasis prophylaxis
Carbonic anhydrase inhibitors • Acetazolamide	• Inhibits carbonic anhydrase enzyme in the proximal tubule	• Hypokalemia • Metabolic acidosis	• Refractory metabolic alkalosis • Intracranial hypertension
Sodium channel blockers • Amiloride • Triamterene	• Inhibits the apical ENaC channel in the cortical collecting duct	• Hyperkalemia • Metabolic acidosis	• Often used in synergy with loop & thiazide diuretics to limit potassium loss
Mineralocorticoid receptor antagonists • Spironolactone	• Inhibits the apical ENaC channel & basolateral Na-K-ATPase pump in the cortical	• Hyperkalemia • Metabolic	

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Carbonic anhydrase inhibitors • Acetazolamide	• Inhibits carbonic anhydrase enzyme in the proximal tubule	• Hypokalemia • Metabolic acidosis	• Refractory metabolic alkalosis • Intracranial hypertension
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Mineralocorticoid receptor antagonists • Spironolactone • Eplerenone	• Inhibits the apical ENaC channel & basolateral Na-K-ATPase pump in the cortical collecting tubules	• Hyperkalemia • Metabolic acidosis	

Loop diuretics are the most potent type of diuretic, followed by thiazide diuretics. Administration of either agent

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Loop diuretics are the most potent type of diuretic, followed by thiazide diuretics. Administration of either agent initially results in natriuresis. However, continued use leads to significant volume depletion that counteracts the diuretic effect by decreasing glomerular filtration pressure. Reduced pressure natriuresis also decreases distal tubule Na^+ delivery, which is sensed by the macula densa and causes activation of the renin-angiotensin-aldosterone system. Aldosterone then acts on the collecting tubule to enhance Na^+ reabsorption and promote K^+ and H^+ loss. Therefore, **loop and thiazide diuretics** cause **hypokalemia** and **metabolic alkalosis** secondary to volume contraction.

Loop diuretics function by inhibiting the absorption of solutes within the thick ascending limb of Henle's loop, a process that is critical for maintenance of the corticomedullary concentration gradient. As a result, patients on loop diuretics are unable to maximally concentrate their urine and thus lose substantial amounts of both salt and water in the urine. In contrast, patients taking thiazides have a normal corticomedullary concentration gradient and are better able to retain free water in response to increased vasopressin levels. Thus, patients taking **thiazide diuretics** are more likely to retain free water and develop **hyponatremia**.

Thiazide diuretics can also lead to **hypercalcemia** secondary to increased proximal and distal tubule Ca^{2+} reabsorption. In contrast, loop diuretics decrease Ca^{2+} reabsorption in the thick ascending limb and can cause hypocalcemia **(Choice E)**.

(Choice A) Acetazolamide induces a mild degree of natriuresis by inhibiting bicarbonate reabsorption in the proximal tubule. The loss of bicarbonate in the urine also causes metabolic acidosis in addition to inducing natriuresis.

(Choices B and D) Amiloride and spironolactone are potassium-sparing diuretics that induce a mild degree of natriuresis. By decreasing Na^+ reabsorption in the cortical collecting tubule, they reduce the luminal electronegative gradient, a major driving force for K^+ and H^+ secretion by principal and intercalated cells, respectively. As a result, potassium-sparing diuretics can cause hyperkalemia and metabolic acidosis.

Educational objective:

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Educational objective:
Thiazide and loop diuretics cause significant volume depletion, activating the renin-angiotensin-aldosterone system, which can lead to hypokalemia and metabolic alkalosis. Thiazide diuretics are more likely to cause hyponatremia and hypercalcemia; loop diuretics cause hypocalcemia.

References

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An 86-year-old man is hospitalized for a complicated hip fracture requiring surgical repair following a fall. His medical problems include prostate cancer, gout, and osteoarthritis. An indwelling urinary catheter is placed due to initial urinary retention and immobilization following the surgery. On the eighth day of hospitalization, the patient develops fever and altered mental status. After evaluation and laboratory testing, a urinary tract infection is diagnosed. Which of the following is the most effective strategy for preventing this complication?

- A. Antibiotic-coated urinary catheter
- B. Bladder irrigation
- C. Prompt removal of catheter when no longer indicated
- D. Prophylactic antibiotics
- E. Routine replacement of catheter

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- A. Antibiotic-coated urinary catheter (2%)
- ✗ B. Bladder irrigation (1%)
- ✓ C. Prompt removal of catheter when no longer indicated (69%)
- D. Prophylactic antibiotics (9%)
- E. Routine replacement of catheter (17%)

Incorrect
Correct answer
C

69%
Answered correctly

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Explanation

Catheter-associated urinary tract infection (UTI) is a frequent complication in hospitalized patients. Common symptoms are fever and pyuria. Suprapubic, flank, and costovertebral tenderness and new-onset altered mental status (delirium) can also occur. The diagnosis is based on a positive urine culture and ruling out other systemic infections (eg, pneumonia). **Duration of catheterization is the most significant risk factor for UTI**. Preventive measures include avoiding unnecessary catheterization, using sterile technique when inserting the catheter, and removing the catheter promptly when no longer needed.

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(Choice A) Antibiotic-coated urinary catheters are costly and have not shown consistent benefit in reducing the risk for UTI.

(Choice B) Bladder irrigation is reserved for patients with hematuria and blood clots and does not prevent UTI.

(Choice D) Prophylactic antibiotics have not been shown to reduce risk of catheter-associated UTI and are associated with development of antibiotic-resistant strains.

(Choice E) Although replacing an indwelling catheter can cause a short-lived reduction in urine bacterial load, it does not confer any clear benefit. Routine replacement of indwelling catheters to prevent infection is not helpful, and catheters should be changed only for specific indications (eg, active infection, obstruction).

Educational objective:
Urinary tract infections (UTIs) are common in hospitalized patients with indwelling urinary catheters. The risk for UTI can be reduced by avoiding unnecessary catheterization, using sterile technique when inserting the catheter, and removing the catheter as soon as possible.

References

- Role of duration of catheterization and length of hospital stay on the rate of catheter-related hospital-acquired urinary tract infections.
- Nosocomial urinary tract infections: A review.

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A 35-year-old man who works as a nurse at a local hospital is brought to the emergency department due to confusion and lethargy. His temperature is 36.7 C (98 F), blood pressure is 86/48 mm Hg, pulse is 120/min, and respirations are 12/min. Arterial blood gas results show pH 7.54, $PaCO_2$ 49 mm Hg, and PaO_2 85 mm Hg. Which of the following laboratory studies would be the most useful in determining the cause of this patient's acid-base abnormality?

- A. Serum ketones
- B. Serum osmolality
- C. Serum sodium
- D. Urine chloride
- E. Urine glucose

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- A. Serum ketones (8%)
- ✗ B. Serum osmolality (23%)
- C. Serum sodium (21%)
- ✓ D. Urine chloride (42%)
- E. Urine glucose (3%)

Incorrect
Correct answer
D

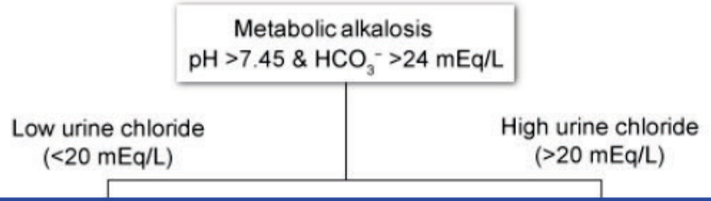
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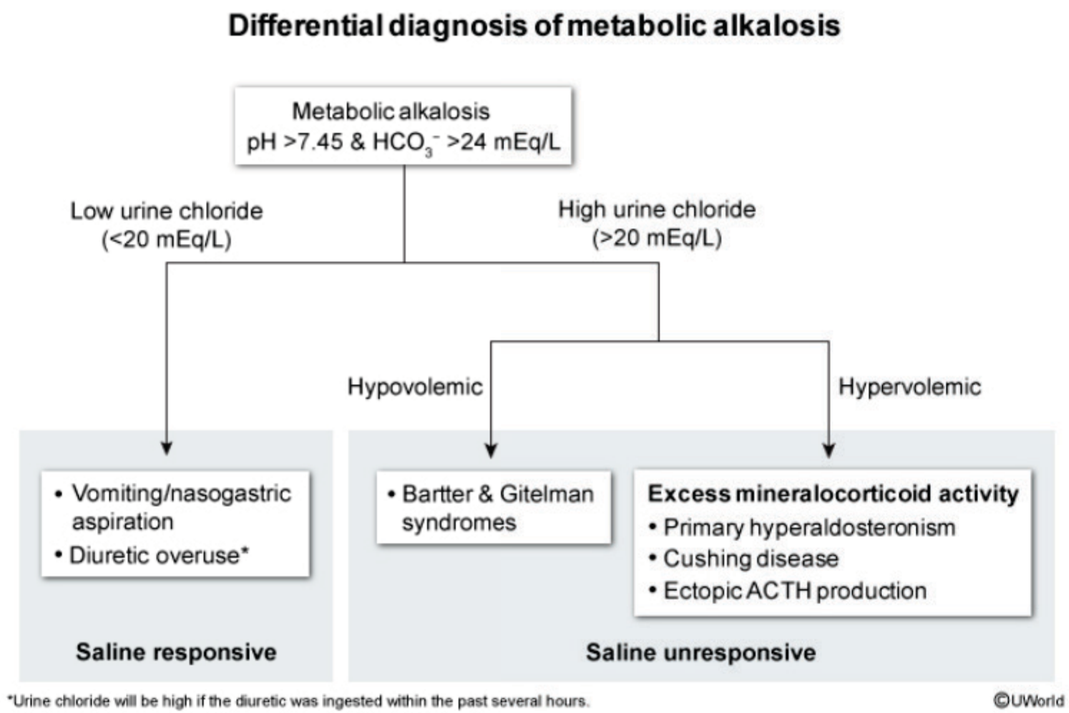
Differential diagnosis of metabolic alkalosis



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E. Urine glucose (3%)

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respiratory acidosis, which does not explain the alkalemia. Therefore, **primary metabolic alkalosis with respiratory compensation** is most likely present. When the etiology of metabolic alkalosis is unknown

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Saline responsive	**Saline unresponsive**

*Urine chloride will be high if the diuretic was ingested within the past several hours.

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This patient's arterial pH >7.45 is consistent with alkalemia. The $PaCO_2$ is elevated (>40 mm Hg), indicating a respiratory acidosis, which does not explain the alkalemia. Therefore, **primary metabolic alkalosis with respiratory compensation** is most likely present. When the etiology of metabolic alkalosis is unknown, assessment of **volume status** and measurement of **urine chloride** can be helpful.

Because low Cl^- impairs renal excretion of HCO_3^-, total body **chloride depletion** often plays an important role in the pathogenesis of metabolic alkalosis. Etiologies of metabolic alkalosis that involve temporary chloride depletion (**hypovolemia**) will demonstrate **low urine chloride** and are amenable to treatment with Cl^- repletion (**saline responsive**). These etiologies include:

- **Nasogastric suctioning** or **severe vomiting**, which involve loss of H^+ and Cl^- (ie, hydrochloric acid) from the stomach.
- **Loop or thiazide diuretic overuse**, which involve loss of Cl^- and retention of HCO_3^- by the kidneys. Of note, urine chloride will be high with recent use but drops to low levels once the diuretic effect wanes.

Metabolic alkalosis can also occur in the absence of significant chloride depletion. Conditions of **mineralocorticoid excess** (eg, primary hyperaldosteronism) cause metabolic alkalosis primarily due to aldosterone-mediated H^+ loss from the kidneys. These patients have **hypervolemia** (eg, hypertension), resulting in a pressure natriuresis with **high urine chloride** levels; the metabolic alkalosis does not correct with Cl^- repletion (**saline unresponsive**) due to the persistent mineralocorticoid effect.

Certain renal tubular channelopathies (eg, Bartter and Gitelman syndromes) represent a special case. Although affected patients are hypovolemic and total body chloride is low, high urine chloride is present because the defect persistently impairs renal Cl- reabsorption.

(Choices A and E) Assessment of serum ketones and urine glucose is helpful in the evaluation of diabetic ketoacidosis as a cause of metabolic acidosis. However, this patient has metabolic alkalosis.

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stomach.

- **Loop or thiazide diuretic overuse**, which involve loss of Cl^- and retention of HCO_3^- by the kidneys. Of note, urine chloride will be high with recent use but drops to low levels once the diuretic effect wanes.

Metabolic alkalosis can also occur in the absence of significant chloride depletion. Conditions of **mineralocorticoid excess** (eg, primary hyperaldosteronism) cause metabolic alkalosis primarily due to aldosterone-mediated H^+ loss from the kidneys. These patients have **hypervolemia** (eg, hypertension), resulting in a pressure natriuresis with **high urine chloride** levels; the metabolic alkalosis does not correct with Cl^- repletion (**saline unresponsive**) due to the persistent mineralocorticoid effect.

Certain renal tubular channelopathies (eg, Bartter and Gitelman syndromes) represent a special case. Although affected patients are hypovolemic and total body chloride is low, high urine chloride is present because the defect persistently impairs renal Cl- reabsorption.

(Choices A and E) Assessment of serum ketones and urine glucose is helpful in the evaluation of diabetic ketoacidosis as a cause of metabolic acidosis. However, this patient has metabolic alkalosis.

(Choices B and C) Intravascular volume depletion can also contribute to metabolic alkalosis by increasing renal bicarbonate reabsorption. However, *serum sodium concentration* is an indication of the relative amounts of total body sodium and total body water; it provides *little information about overall volume status* (ie, hypo- or hypernatremia can occur with hypovolemia, euvolemia, or hypervolemia). Serum osmolality usually reflects serum sodium concentration unless high levels of other osmotically active substances are present (eg, glucose, ethanol); like serum sodium, it cannot be used to reliably differentiate hypovolemia from hypervolemia.

Educational objective:
Total body chloride depletion is often important in the pathophysiology of metabolic alkalosis. Measurement of urine chloride can be helpful in determining the underlying etiology.

References

- Metabolic alkalosis.

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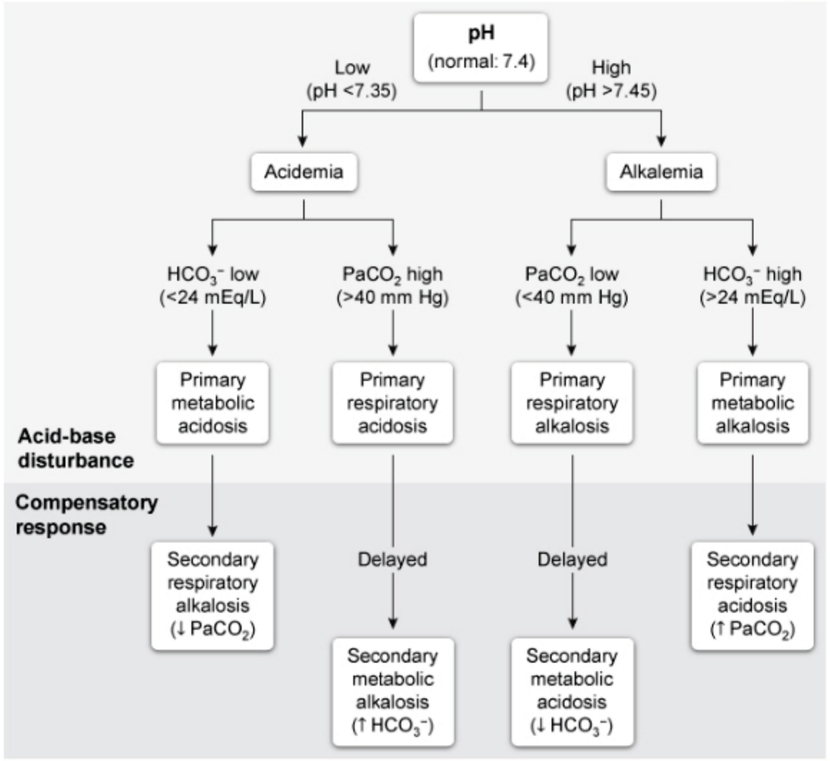
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syndromes

• Primary hyperaldosteronism

Exhibit Display

Arterial blood gas interpretation of acid-base disorders



* The normal ranges for $PaCO_2$ and HCO_3^- vary slightly around 40 mm Hg and 24 mEq/L.
For simplicity, these numbers should be used as a normal baseline for acid-base calculations.

HCO_3^- = bicarbonate; **$PaCO_2$** = partial pressure of carbon dioxide in arterial blood.

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Certain renal tubular channelopathies (eg, Bartter and Gitelman syndromes) represent a special case. Although affected patients are hypovolemic and total body chloride is low, high urine chloride is present because the defect

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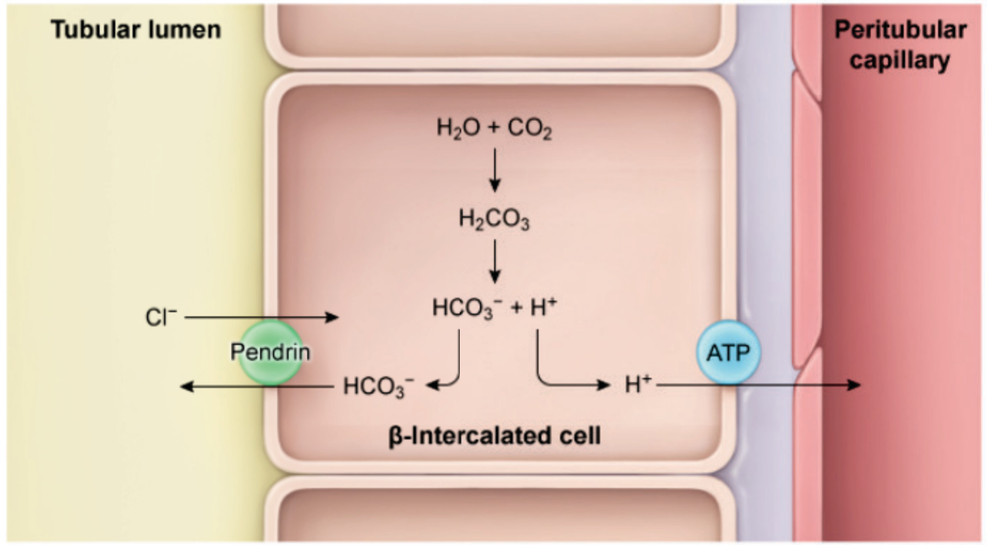
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Pendrin chloride/bicarbonate exchanger



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affected patients are hypovolemic and total body chloride is low, high urine chloride is present because the defect

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A 43-year-old man comes to the office due to swelling of the legs and abdomen. The patient has a history of alcohol-induced cirrhosis, and his ascites had been well controlled with furosemide. Over the past week, he has had increasing bilateral lower extremity and abdominal swelling despite taking a diuretic as prescribed. The patient reports no change in dietary sodium or water intake but states he has been taking over-the-counter ibuprofen after injuring his back recently. He stopped drinking alcohol 2 years ago and does not use tobacco or illicit drugs. Physical examination shows 3+ bilateral lower extremity edema and moderate ascites. Which of the following changes most likely contributed to the acute deterioration in this patient's condition?

	Renal prostaglandin level	Glomerular filtration rate	Urinary sodium excretion
○ A.	Decreased	Decreased	Decreased
○ B.	Decreased	Unchanged	Decreased
○ C.	Increased	Increased	Increased
○ D.	Increased	Increased	Unchanged
○ E.	Unchanged	Decreased	Increased

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	Renal prostaglandin level	Glomerular filtration rate	Urinary sodium excretion	
✓ A.	Decreased	Decreased	Decreased	(88%)
B.	Decreased	Unchanged	Decreased	(5%)
C.	Increased	Increased	Increased	(1%)
D.	Increased	Increased	Unchanged	(2%)
E.	Unchanged	Decreased	Increased	(2%)

Correct

88% Answered correctly

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Explanation

Furosemide is a loop diuretic that binds to Na-K-2Cl symporters in the ascending limb of the loop of Henle and effectively blocks Na and Cl transport, resulting in increased Na, Cl, and fluid excretion. Loop diuretics also

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Furosemide is a loop diuretic that binds to Na-K-2Cl symporters in the ascending limb of the loop of Henle and effectively blocks Na and Cl transport, resulting in increased Na, Cl, and fluid excretion. Loop diuretics also **stimulate prostaglandin release**, which increases renal plasma flow (RPF), leading to increased glomerular filtration rate (GFR) and drug delivery to the loop of Henle.

Nonsteroidal anti-inflammatory drugs (NSAIDs) (eg, ibuprofen, naproxen, indomethacin) **inhibit prostaglandin synthesis** (resulting in decreased renal prostaglandin levels). In healthy patients, prostaglandin synthesis is low and NSAID use has minimal effects on renal hemodynamics. However, patients with intravascular volume depletion (eg, **cirrhosis**, congestive heart failure, dehydration) are dependent on the vasodilatory effects of prostaglandins to maintain adequate RPF and GFR.

Therefore, NSAID use in this population leads to markedly **decreased GFR and RPF**. Reduced fluid and electrolyte delivery to renal tubules reduces the efficacy of loop diuretics, resulting in **reduced urinary sodium excretion** and fluid retention (eg, ascites, edema, as occurred in this patient). Similar effects can occur in patients with chronic kidney disease; therefore, NSAIDs should generally be avoided in all patients with renal disease or reduced effective arterial volume.

(Choices B, C, D, and E) NSAIDs inhibit prostaglandin synthesis, resulting in renal vasoconstriction and decreased GFR. This limits the efficacy of loop diuretics, leading to reduced urinary sodium excretion and fluid retention (promoting the formation of ascites and edema).

Educational objective:
Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin synthesis. Patients with intravascular volume depletion (eg, cirrhosis) are dependent on the vasodilatory effects of prostaglandins to maintain adequate renal plasma flow and glomerular filtration. NSAID use in this population reduces glomerular filtration rates and blunts the effects of loop diuretics, leading to sodium and water retention.

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A 44-year-old man comes to the hospital due to acute onset of central chest pain radiating to the left arm. He used cocaine a few hours ago. Blood pressure is 160/100 mm Hg, pulse is 98/min, and respirations are 18/min. On examination, the patient appears anxious and diaphoretic. Electrocardiogram shows ST-segment elevation in the anterior leads. Laboratory studies reveal an elevated cardiac troponin level and a serum potassium concentration of 3.1 mEq/L. Which of the following is the most likely cause of this patient's hypokalemia?

- A. Decreased dietary potassium intake
- B. Exchange of potassium with sodium in the intestine
- C. Increased intracellular shift of potassium
- D. Increased urinary loss of potassium
- E. Increased use of potassium by new cells

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- A. Decreased dietary potassium intake (1%)
- ✗ B. Exchange of potassium with sodium in the intestine (3%)
- ✓ C. Increased intracellular shift of potassium (71%)
- D. Increased urinary loss of potassium (22%)
- E. Increased use of potassium by new cells (2%)

Incorrect
Correct answer
C

71%
Answered correctly

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Time Spent

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Explanation

Causes of hypokalemia	
Decreased intake	• Starvation, anorexia
Intracellular translocation	• Insulin (eg, treatment of DKA, refeeding syndrome) • β-adrenergic activity ◦ Pharmacologic (eg, albuterol, dobutamine)

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Causes of hypokalemia	
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Gastrointestinal loss	• Diarrhea, vomiting, hyperaldosteronism
Urinary loss	• Hyperaldosteronism, diuretics, RTA types 1 and 2
Sweat loss	• Extreme exercise in hot climate
DKA = diabetic ketoacidosis; **MI** = myocardial infarction; **GM-CSF** = granulocyte-macrophage colony-stimulating factor; **RTA** = renal tubular acidosis.	

Low serum potassium is a common medical condition that can result from several mechanisms, including decreased oral intake, renal or gastrointestinal loss, or increased entry into cells. This patient with a cocaine-induced **myocardial infarction** most likely developed **acute hypokalemia** due to stress-related **beta-adrenergic hyperactivity**, which causes potassium to shift intracellularly.

Severe physiologic stress (eg, myocardial infarction, head injury) results in significant endogenous catecholamine (eg, norepinephrine, epinephrine) release. Epinephrine activates the **beta-2 receptor**, leading to increased activity of the sodium-potassium ATPase pump and the sodium-potassium-2-chloride cotransporter, both of which **transport potassium intracellularly**. Adrenergic activity also stimulates the release of insulin, which further promotes intracellular potassium shifting. Although cocaine does not directly stimulate beta-2 receptors, it does

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Similar intracellular shifts can be seen with beta-agonist medications (eg, albuterol, dobutamine) and sympathomimetics (eg, pseudoephedrine). Patients with other sources of potassium loss (eg, diuretics, diarrhea) are at increased risk.

(Choice A) Hypokalemia due to decreased dietary intake of potassium typically occurs in patients with very poor oral intake (eg, anorexia, starvation, malignancy).

(Choice B) Significant gastrointestinal potassium loss can occur with prolonged diarrhea or use of gastrointestinal cation exchangers that bind potassium in exchange for other cations (eg, sodium, calcium).

(Choice D) Increased urinary potassium loss can occur with diuretic use and in the setting of elevated aldosterone levels (eg, renovascular disease, primary aldosteronism). Although hyperaldosteronism is associated with hypertension, this patient's elevated blood pressure is likely from cocaine use.

(Choice E) Increased potassium uptake by cells during accelerated hematopoiesis (eg, administration of granulocyte-macrophage colony-stimulating factor, acute leukemia) may cause hypokalemia. However, this patient does not have these risk factors.

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(Choice E) Increased potassium uptake by cells during accelerated hematopoiesis (eg, administration of granulocyte-macrophage colony-stimulating factor, acute leukemia) may cause hypokalemia. However, this patient does not have these risk factors.

Educational objective:
Hypokalemia can result from the intracellular shift of potassium, which can occur due to beta-adrenergic hyperactivity (eg, beta-2 agonists, endogenous epinephrine release), increased insulin levels, elevated extracellular pH, or increased cell production (eg, acute leukemia).

Physiology	Renal, Urinary Systems & Electrolytes	Hypokalemia
Subject	System	Topic

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A 28-year-old man is hospitalized following a motor vehicle collision complicated by severe hemorrhage. Over the next 8 hours his urine output is markedly decreased. Laboratory results reveal elevated blood urea nitrogen. The patient is given aggressive intravenous fluid hydration. After 24 hours of therapy, urine output is increased and blood urea nitrogen declines toward normal. Which of the following additional laboratory abnormalities suggests that this patient's initial oliguria is a compensation for volume contraction?

- A. Muddy brown casts on urinalysis
- B. Serum BUN/creatinine ratio <15
- C. Urine fractional excretion of sodium >2%
- D. Urine osmolarity <350 mOsm/kg
- E. Urine sodium <20 mEq/L

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- A. Muddy brown casts on urinalysis (8%)
- ✗ B. Serum BUN/creatinine ratio <15 (9%)
- C. Urine fractional excretion of sodium >2% (12%)
- D. Urine osmolarity <350 mOsm/kg (7%)
- ✓ E. Urine sodium <20 mEq/L (62%)

Incorrect
Correct answer
E

62%
Answered correctly

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Explanation

Acute kidney injury		
	Prerenal	**Acute tubular necrosis**
Mechanism	Decreased renal perfusion (eg, hypovolemia, CHF)	Renal ischemia (eg, hemorrhage, sepsis) or nephrotoxins (eg, aminoglycosides, radiocontrast)

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Mechanism	Decreased renal perfusion (eg, hypovolemia, CHF)	Renal ischemia (eg, hemorrhage, sepsis) or nephrotoxins (eg, aminoglycosides, radiocontrast)
BUN/creatinine ratio	Typically >20	Typically ~10-15
Fractional excretion of sodium	<1%	>2%
Urine osmolality	>500 mOsm/kg	~300 mOsm/kg
Microscopy	Hyaline casts	Muddy brown casts
BUN = blood urea nitrogen; **CHF** = congestive heart failure.		

This patient developed symptoms of acute renal failure (ARF) (eg, low urine output, high blood urea nitrogen) after a massive hemorrhage. ARF can be classified according to 1 of 3 etiologies:

- **Prerenal:** Caused by **decreased renal perfusion**; the nephrons remain intact and tubular function is preserved. Etiologies include volume loss (eg, hemorrhage), low-output states (eg, myocardial infarction, congestive heart failure), or systemic vasodilation (eg, sepsis).
- **Intrinsic:** Caused by **tubular epithelial or glomerular damage**; resorptive capacity is lost. Etiologies include acute tubular necrosis (due to renal ischemia or nephrotoxins) or glomerular diseases (eg, glomerulonephritis, nephrotic syndrome).
- **Postrenal:** Caused by **urinary tract obstruction** with normal nephron capacity. Etiologies include bilateral calculi, enlarged prostate, or a renal tumor in an individual with a sole functional kidney.

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- **Postrenal:** Caused by **urinary tract obstruction** with normal nephron capacity. Etiologies include bilateral calculi, enlarged prostate, or a renal tumor in an individual with a sole functional kidney.

This patient with severe blood loss was at risk for prerenal and intrinsic renal failure; however, his rapid **improvement with hydration** suggests a prerenal (hypovolemic) etiology. His laboratory results reflect intact renal tubular function, with compensatory mechanisms to restore blood volume. Increased tubular sodium reabsorption results in **low urine sodium (<20 mEq/L)** and **low fractional excretion of sodium** (FENa), whereas increased water reabsorption leads to **high urine osmolarity**. Urea reabsorption also increases to help concentrate the urine, resulting in increased serum levels of urea; creatinine continues to be excreted, resulting in the characteristic **BUN/creatinine ratio >20**.

In contrast, intrinsic ARF reflects tubular epithelium damage and loss of renal reabsorptive capacity. Water, sodium, and urea are excreted in the urine, leading to lower urine osmolarity, higher urinary sodium, higher urinary FENa, and a normal serum BUN/creatinine ratio.

(Choice A) Dark, granular, "muddy brown" casts seen on urinalysis are composed of degenerating tubular epithelial cells. This finding is associated with acute tubular necrosis, which is a common cause of intrinsic ARF.

(Choices B, C, and D) A serum BUN/creatinine ratio <15, urine FENa >2%, and urine osmolarity <350 mOsm/kg

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(Choices B, C, and D) A serum BUN/creatinine ratio <15, urine FENa >2%, and urine osmolarity <350 mOsm/kg are characteristic of intrinsic ARF. These alterations in the laboratory indices of renal function represent the diminished ability of tubular epithelial cells to reabsorb urea, sodium, and water, respectively.

Educational objective:
Blood volume loss can cause prerenal or intrinsic acute renal failure (ARF). Prerenal ARF is associated with normal nephron function (eg, low urine sodium level, low fractionated sodium excretion, high urine osmolarity, and a high BUN/creatinine ratio), whereas intrinsic ARF features diminished renal reabsorptive capacity (eg, lower urine osmolarity, higher urinary sodium, normal serum BUN/creatinine ratio).

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A 54-year-old missionary traveling alone in a remote region of Southern Asia becomes lost. After several days, he arrives at a small village. However, he has gone 24 hours without food or water, and his urine osmolarity is 1150 mOsm/L. The majority of the total amount of water filtered by this individual's glomeruli is reabsorbed in which of the following portions of the nephron?

- A. Cortical collecting duct
- B. Distal tubule
- C. Loop of Henle
- D. Medullary collecting duct
- E. Proximal tubule

Submit

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- A. Cortical collecting duct (16%)
- ✗ B. Distal tubule (3%)
- C. Loop of Henle (10%)
- D. Medullary collecting duct (30%)
- ✓ E. Proximal tubule (38%)

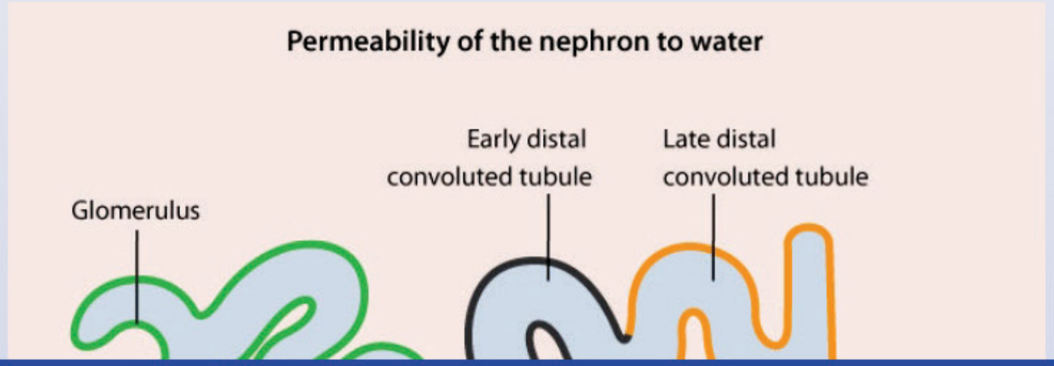
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Correct answer
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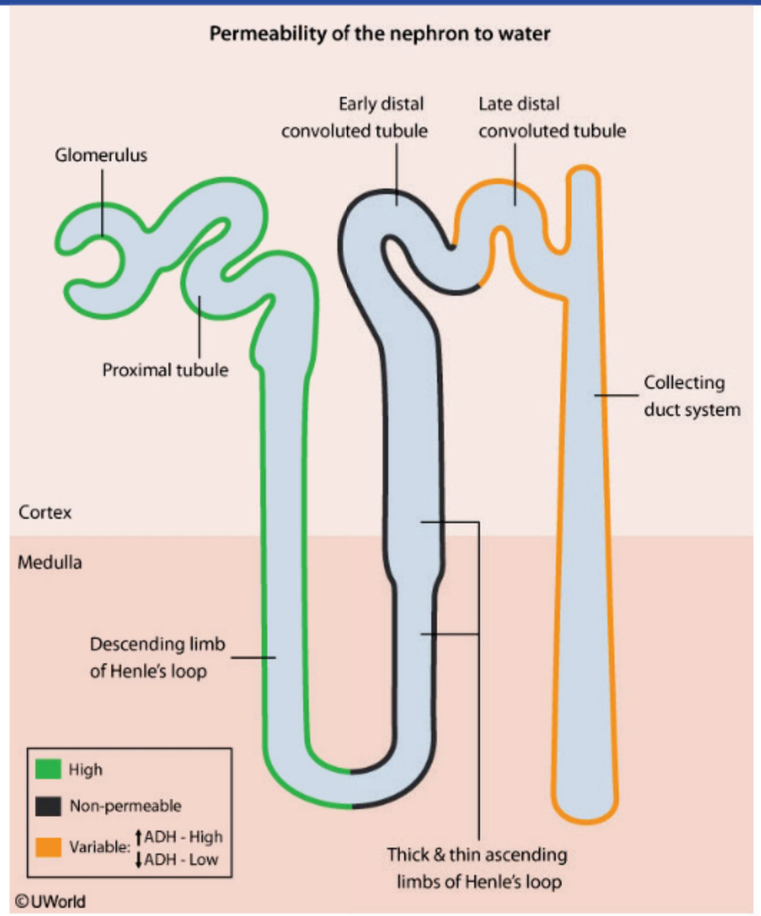
Explanation



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A 54-year-old missionary traveling alone in a remote region of Southern Asia becomes lost. After several days, he arriv
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The **proximal tubules reabsorb >60%** of the water filtered by the glomeruli, regardless of the patient's hydration status. This water is reabsorbed isosmotically with solutes (eg, Na^+, Cl^-, glucose); no concentration or dilution of urine occurs in this segment.

In the dehydrated state, plasma osmolarity increases, stimulating osmoreceptors in the anterior hypothalamus. This triggers increased **antidiuretic hormone** (ADH) synthesis and release into the circulation. ADH then acts on the kidney to improve the water permeability of the collecting ducts, allowing production of maximally concentrated urine (osmolarity of 1200 mOsm/L). This increase in urine concentration with water deprivation reflects that the kidneys are functioning properly to conserve water. However, without eventual fluid replenishment, dehydration will ultimately progress to death because even at maximum resorptive capacity, the kidney still produces approximately 0.5 L of urine per day.

(Choice C) Urine concentration increases in the water-permeable descending loop of Henle due to the increasing osmolarity of the corticopapillary gradient in the renal interstitium; this segment normally reabsorbs about 20% of the filtered water volume.

(Choices A, B, and D) In the dehydrated state, ADH promotes aquaporin (water channel) insertion into the apical membranes of the principal cells lining the late distal tubules and collecting ducts. Up to 20% of the original filtered volume of water can be reabsorbed here, allowing >99% of filtered water to be resorbed by the nephron during dehydration. No water is reabsorbed in these segments in the overhydrated state.

Educational objective:
Regardless of the patient's hydration status, the majority of water reabsorption in the nephron occurs in the proximal tubule passively with the reabsorption of solutes.

Physiology	Renal, Urinary Systems & Electrolytes	Hypovolemia
Subject	System	Topic

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A 40-year-old nulligravida woman comes to the office with a 2-month history of worsening right pelvic pain. She experiences the pain daily, and its intensity does not vary during her menstrual cycle. In addition, the patient's waist size has increased despite a decreased appetite. Pelvic examination shows an irregularly shaped, fixed adnexal mass. One week later, she undergoes surgery to remove a large ovarian neoplasm. Within the true pelvis, the surgeon can most likely palpate the right ureter immediately anterior to which of the following structures?

- A. Gonadal vein
- B. Inferior vena cava
- C. Internal iliac artery
- D. Round ligament
- E. Uterine artery

Submit

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- A. Gonadal vein (9%)
- B. Inferior vena cava (2%)
- ✓ C. Internal iliac artery (43%)
- D. Round ligament (13%)
- E. Uterine artery (30%)

Correct

43%
Answered correctly

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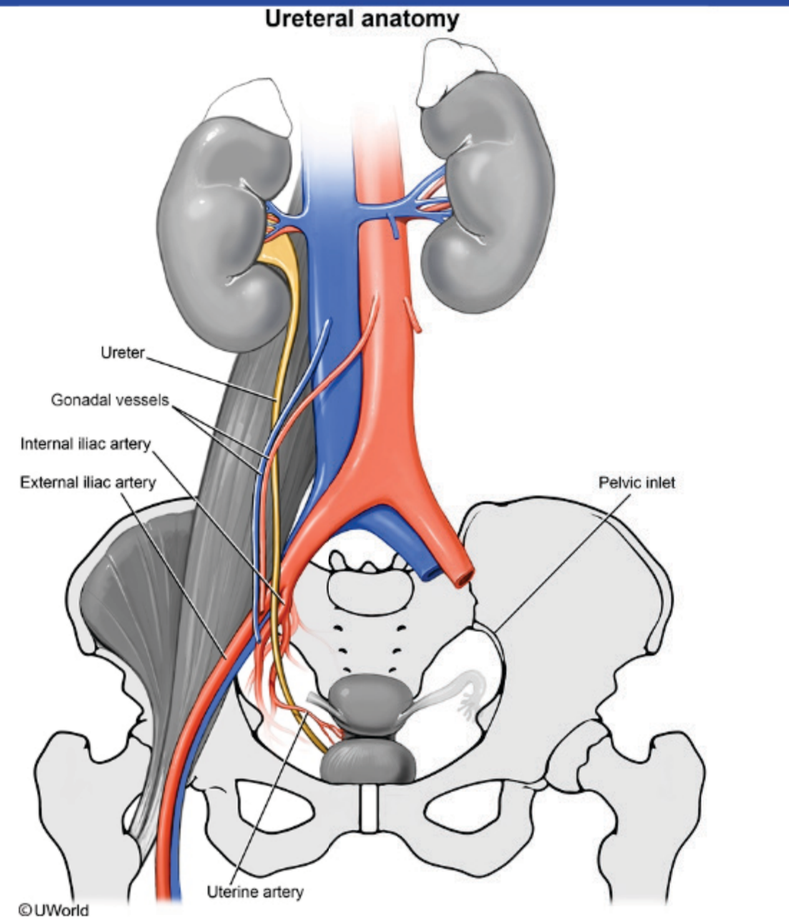
Explanation



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structures?

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The **ureters** originate bilaterally at the renal pelvis and course inferiorly toward the bladder within the retroperitoneum just anterior to the psoas muscles. Midway from the kidney to the pelvic inlet, the ureters cross posterior to the gonadal artery and vein. The ureters then gain access to the pelvis by crossing anterior to the external iliac artery at, or just after, the bifurcation of the common iliac artery. At this point, the ureter lies medial to the ovarian vessels and **anterior to the internal iliac artery**.

Due to their course and proximity to other structures, the ureters are at particular risk for injury during pelvic and abdominal surgery.

(Choice A) The ureters cross posterior to the gonadal vessels within the retroperitoneum before entering the pelvis. In females, the ureters lie within the true pelvis medial to the ovarian vessels. In males, the testicular vessels never enter the true pelvis; instead, they pass around the pelvic brim before entering the deep ring of the inguinal canal.

(Choice B) The inferior vena cava rests on the right side of the vertebral bodies and is formed by the union of the common iliac veins at the L4 level. The internal and external iliac veins join to form the common iliac veins at the pelvic inlet.

(Choice D) The round ligaments of the uterus originate at the uterine fundus and course through the inguinal canal out to the labia majora. The ureters do not lie in close proximity.

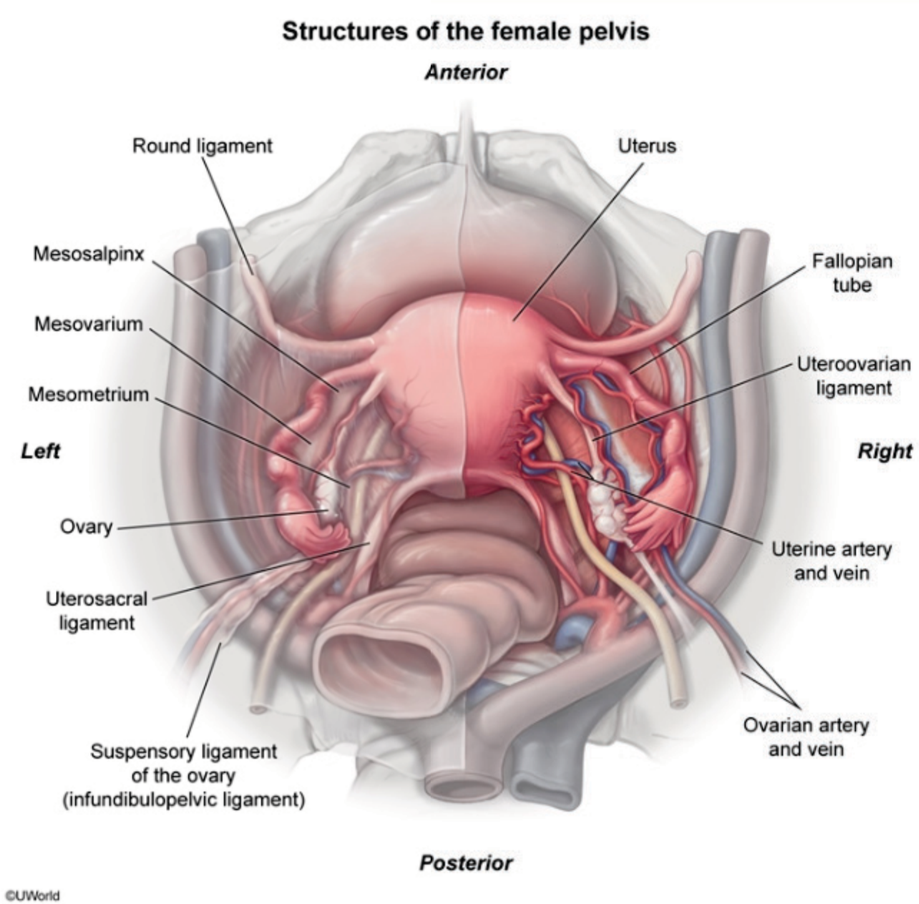
(Choice E) The uterine artery courses within the cardinal ligament to reach the uterus. The ureters course along the uterosacral ligament and cross posterior to the uterine artery ("water under the bridge") before entering the bladder.

Educational objective:
The ureters pass posterior to the ovarian (gonadal) vessels within the retroperitoneum and cross anterior to the common/external iliac arteries to reach the true pelvis. Within the true pelvis, the ureters lie anterior to the internal iliac artery and posterior to the uterine artery.

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The **ureters** originate bilaterally at the renal pelvis and course inferiorly toward the bladder within the retro
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iliac artery and posterior to the uterine artery.

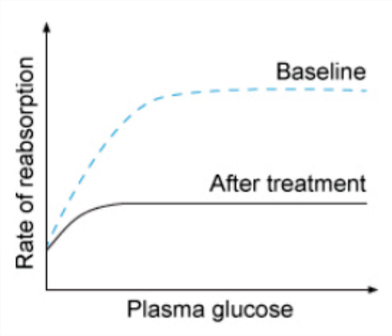
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A 34-year-old healthy woman enrolls in a clinical trial. She receives an intravenous infusion of glucose to achieve various steady-state plasma concentrations. Urinary volume and urinary glucose excretion are measured at different plasma glucose levels. The data are extrapolated to determine the normal (baseline) relationship between plasma glucose concentration and renal glucose reabsorption. The experiment is repeated following administration of the study medication (after treatment). The results are shown in the image below:



Which of the following medications was most likely used in this study?

- A. Canagliflozin
- B. Chlorthalidone
- C. Insulin
- D. Liraglutide
- E. Metformin
- F. Sitagliptin

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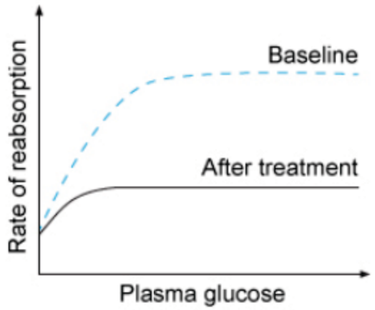
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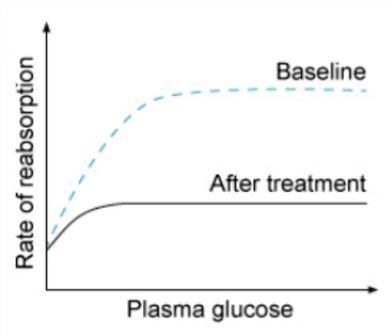
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Which of the following medications was most likely used in this study?

- ✓ A. Canagliflozin (76%)
- B. Chlorthalidone (3%)
- ✗ C. Insulin (4%)
- D. Liraglutide (3%)
- E. Metformin (5%)
- F. Sitagliptin (6%)

Incorrect
Correct answer
A

76%
Answered correctly

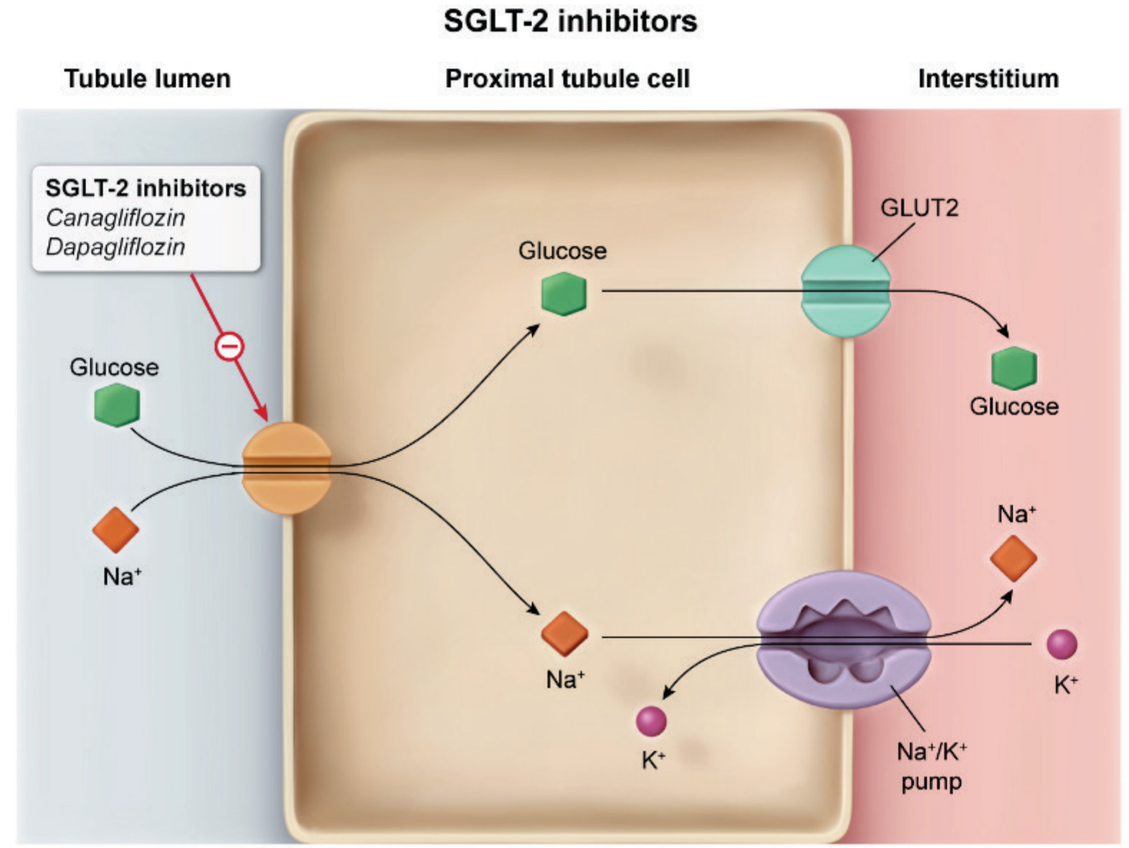
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Explanation

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GLUT2 = glucose transporter 2; **SGLT-2** = sodium-glucose cotransporter 2.

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Glucose is freely filtered at the glomerulus and is promptly reabsorbed in the proximal tubule by a sodium-coupled active transport mechanism (ie, **sodium-glucose cotransporter-2** [SGLT-2]). Normally, nearly all filtered glucose is reabsorbed. However, this reabsorption mechanism is saturable; at higher filtered glucose loads (ie, higher plasma glucose), reabsorption is inadequate to completely retain all of the filtered glucose, and the excess is excreted in the urine.

SGLT-2 inhibitors (eg, canagliflozin) are a class of antidiabetic agents that reduce sodium-coupled glucose reabsorption in the proximal tubule. This **reduces glucose reabsorption** by the kidney (ie, increases urinary glucose loss) and lowers blood glucose levels. Concurrently, the glycosuria causes an **osmotic diuresis** that modestly lowers blood pressure.

As blood glucose falls and the filtered glucose load decreases, glucose reabsorption is again adequate to reabsorb nearly all of the filtered glucose. At normal blood glucose levels, the glucose-lowering effect is minimal; therefore, these agents carry a **low risk** for drug-induced **hypoglycemia**.

(Choice B) Thiazide diuretics (eg, chlorthalidone) decrease reabsorption of sodium, chloride, and water in the distal convoluted tubule. They can cause hyperglycemia by decreasing insulin secretion; however, they do not affect renal glucose reabsorption.

(Choice C) Insulin has a variety of physiologic effects, but it primarily lowers blood glucose by increasing hepatic glycogen synthesis and stimulating glucose uptake in peripheral tissues. It does not alter renal glucose reabsorption.

(Choices D, E, and F) Glucagon-like peptide-1 (GLP-1) agonists (eg, liraglutide) lower blood glucose by increasing glucose-dependent insulin secretion and decreasing glucagon secretion. Metformin lowers glucose levels by decreasing hepatic glucose production and increasing peripheral glucose uptake. Dipeptidyl peptidase-4 inhibitors (eg, sitagliptin) decrease degradation of endogenous GLP-1, leading to similar (though less potent) effects. These drugs do not affect renal glucose reabsorption.

Educational objective:

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excreted in the urine.

SGLT-2 inhibitors (eg, canagliflozin) are a class of antidiabetic agents that reduce sodium-coupled glucose reabsorption in the proximal tubule. This **reduces glucose reabsorption** by the kidney (ie, increases urinary glucose loss) and lowers blood glucose levels. Concurrently, the glycosuria causes an **osmotic diuresis** that modestly lowers blood pressure.

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Educational objective:
Glucose is reabsorbed from the proximal tubule by sodium-glucose cotransporter-2 (SGLT-2). Normally, nearly all filtered glucose is reabsorbed. SGLT-2 inhibitors lower the threshold at which filtered glucose can be fully reabsorbed; this increases urinary glucose losses and lowers blood glucose levels.

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active transport mechanism (ie, **sodium-glucose cotransporter-2** [SGLT-2]). Normally, nearly all filtered glucose

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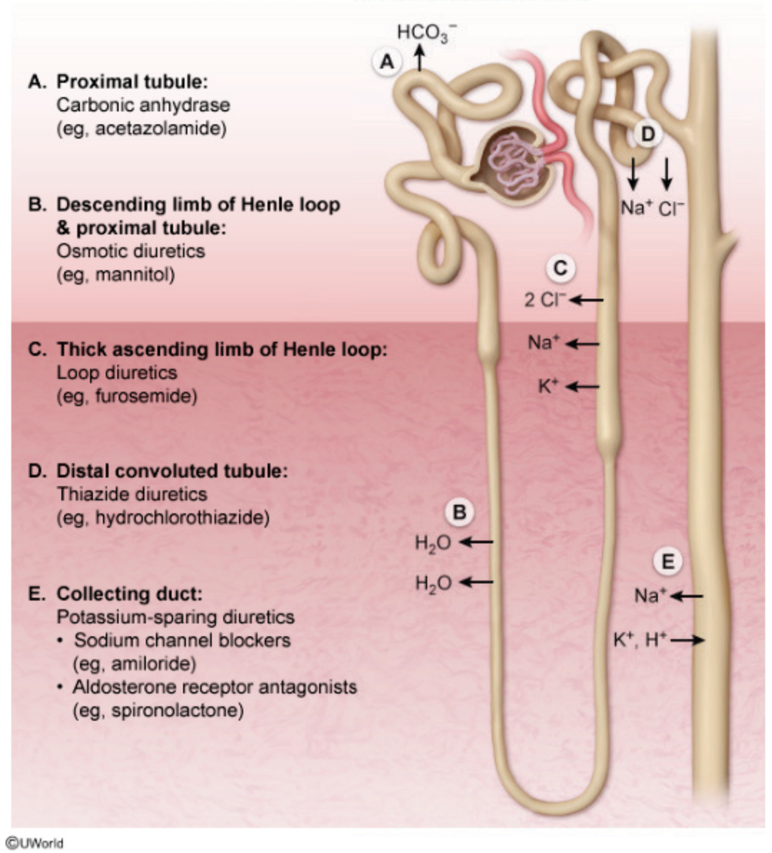
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Site of action for various diuretics



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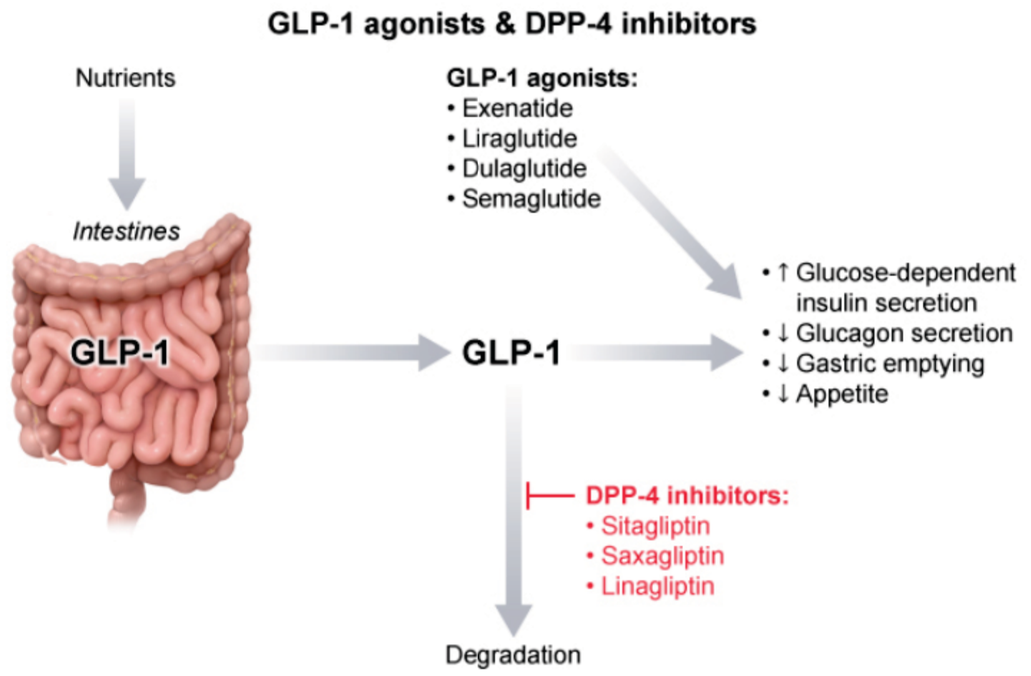
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An 81-year-old woman reports progressively increasing bilateral shoulder pain for 2 months. Over the past 2 weeks, she has developed burning pain in her right thumb, index, and middle fingers. Medical history is significant for type 2 diabetes mellitus and end-stage renal disease due to diabetic nephropathy. The patient has received hemodialysis for the past 10 years. Vital signs are normal. Examination reveals normal heart and lung sounds. There is no organomegaly. Both shoulders are hypertrophied. There is thenar atrophy on the right hand and soft tissue fullness at the right wrist. Which of the following is most likely responsible for this patient's current condition?

- A. Clonal production of excess free immunoglobulin light chains
- B. Cytokine-mediated increased production of amyloid A protein
- C. Tissue deposition of beta2-microglobulin
- D. Tissue deposition of mutated transthyretin
- E. Tissue deposition of wild-type transthyretin

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- A. Clonal production of excess free immunoglobulin light chains (3%)
- ✗ B. Cytokine-mediated increased production of amyloid A protein (16%)
- ✓ C. Tissue deposition of beta2-microglobulin (61%)
- D. Tissue deposition of mutated transthyretin (8%)
- E. Tissue deposition of wild-type transthyretin (9%)

Incorrect
Correct answer
C

61%
Answered correctly

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Explanation

Major types of systemic amyloidosis

	Primary	Secondary	Age related	Dialysis related
Disease	Plasma cell dyscrasia	Chronic infection/	Elderly men	ESRD on dialysis

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Major types of systemic amyloidosis

	Primary	Secondary	Age related	Dialysis related
Disease association	Plasma cell dyscrasia	Chronic infection/ inflammation	Elderly men	ESRD on dialysis
Precursor protein ↓ **Misfolding mechanism** ↓ **Amyloid fibril type**	Immunoglobulin light chains ↓ Increased production ↓ AL	Serum amyloid A ↓ Increased production ↓ AA	Transthyretin (prealbumin) ↓ Accumulation over time ↓ ATTR*	β_2-Microglobulin ↓ Decreased clearance ↓ $A\beta_2M$
Clinical manifestations	Nephropathy, hepatosplenomegaly, cardiomyopathy (AL > AA), peripheral neuropathy, macroglossia, skin bruising		Cardiomyopathy, CTS, other peripheral neuropathy	Scapulohumeral arthritis, CTS

Amyloid names begin with "A" followed by the precursor protein abbreviation.
*ATTR also occurs in a hereditary form that affects younger patients.
CTS = carpal tunnel syndrome; **ESRD** = end-stage renal disease.

This patient on long-term hemodialysis has carpal tunnel syndrome and shoulder pain/hypertrophy, most likely due to **dialysis-related amyloidosis** (DRA).

Amyloidosis is a group of multisystem disorders, all characterized by **misfolded proteins**. Misfolding results from increased production, decreased clearance, inherited mutations, or age-related deposition of protein subunits. Structural transformation of precursor proteins into **beta-pleated sheets** leads to aggregation and polymerization

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Amyloidosis is a group of multisystem disorders, all characterized by **misfolded proteins**. Misfolding results from increased production, decreased clearance, inherited mutations, or age-related deposition of protein subunits. Structural transformation of precursor proteins into **beta-pleated sheets** leads to aggregation and polymerization into amyloid fibrils. Resistant to degradation, amyloid **accumulates in extracellular tissues**, causing organ dysfunction. Each precursor protein generates specific amyloid fibrils predisposed to particular organs.

In DRA, **beta2-microglobulin** (beta2-m) is the precursor protein and a component of major histocompatibility class I molecules on all nucleated cells. Continuously shed in plasma, beta2-m has near-total clearance by normal kidneys. However, in end-stage renal failure, it is **inadequately eliminated despite dialysis** and deposited in tissue as beta2-m amyloid. Disease most often involves **osteoarticular structures** as connective tissue components (eg, glycosaminoglycans, type-1 collagen) stabilize beta2-m amyloid fibrils and inhibit their depolymerization. Typical manifestations include:

- Scapulohumeral periarthritis (pain/hypertrophy from rotator cuff infiltration)
- Carpal tunnel syndrome (median neuropathy from carpal tunnel deposition)
- Flexor tenosynovitis (contractures from involvement of flexor tendons)
- Bone cysts (possible pathologic fractures)

DRA prevalence increases with age and dialysis duration. Although improved dialysis membranes provide better clearance of beta2-m, its prevalence remains significant.

(Choice A) Free immunoglobulin light chains are produced in excess by clonal expansion of plasma cells in multiple myeloma and deposited as AL amyloid. AL amyloid typically results in nephrotic syndrome, hepatomegaly, restrictive cardiomyopathy, and neuropathy. Macroglossia and periorbital purpura are less common but characteristic.

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tissue as beta2-m amyloid. Disease most often involves **osteoarticular structures** as connective tissue components (eg, glycosaminoglycans, type-1 collagen) stabilize beta2-m amyloid fibrils and inhibit their depolymerization. Typical manifestations include:

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(Choice B) Serum amyloid A is an acute phase protein excessively produced due to elevated cytokines in chronic infectious or inflammatory conditions (eg, tuberculosis, rheumatoid arthritis). Accumulation produces AA amyloid, which deposits primarily in the kidneys, liver, and spleen. This patient has no chronic infectious or inflammatory conditions.

(Choices D and E) Transthyretin is a protein named for its function (*trans*ports *thy*roxin and *retin*ol). Inherited mutation or age can cause its deposition as amyloid with prominent cardiac involvement.

Educational objective:
Beta2-microglobulin is renally cleared and poorly dialyzed. It accumulates as amyloid in dialysis patients, increasing in prevalence with dialysis duration, and has a predilection for osteoarticular surfaces. Shoulder pain and carpal tunnel syndrome are common. Bone cysts and pathologic fractures may also occur.

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Structural transformation of precursor proteins into **beta-pleated sheets** leads to aggregation and polymerization into dysf

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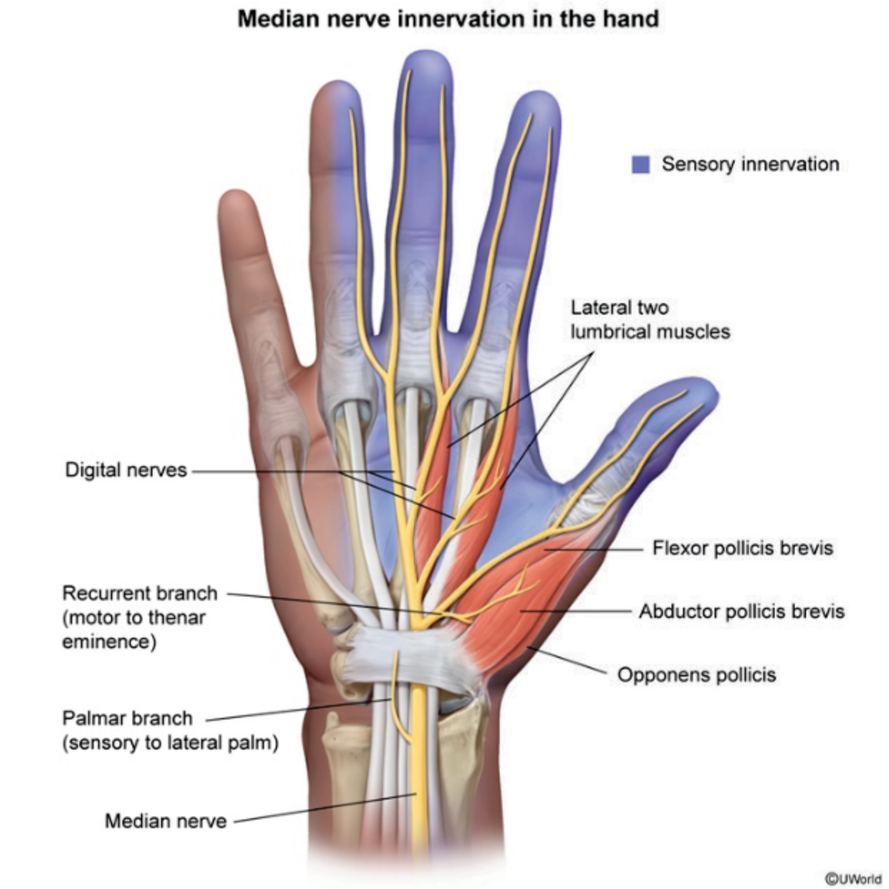
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(Choices D and E) Transthyretin is a protein named for its function (*trans*ports *thy*roxin and *retin*ol). Inherited

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A 17-year-old previously healthy girl is brought to the office by her mother after an episode of severe light-headedness. The patient has had no syncope, chest pain, shortness of breath, or palpitations but reports frequent muscle cramps. The mother has noted that the patient is using the bathroom more frequently and says that her daughter has recently been more concerned about her body size. When interviewed alone, the patient says she has been taking several laxatives in an attempt to lose weight but has not performed self-induced vomiting. Which of the following laboratory findings are most likely present in this patient?

	Serum potassium	Serum bicarbonate	Aldosterone
○ A.	Decreased	Decreased	Decreased
○ B.	Decreased	Increased	Increased
○ C.	Increased	Decreased	Decreased
○ D.	Increased	Decreased	Normal
○ E.	Increased	Increased	Increased

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	Serum potassium	Serum bicarbonate	Aldosterone	
A.	Decreased	Decreased	Decreased	(20%)
✓ B.	Decreased	Increased	Increased	(46%)
C.	Increased	Decreased	Decreased	(10%)
D.	Increased	Decreased	Normal	(15%)
E.	Increased	Increased	Increased	(3%)

Correct

46%
Answered correctly

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Explanation

This patient's light-headedness, muscle cramps, and increased bathroom use are likely due to **diarrhea** caused by **laxative misuse**. Laxatives increase secretion of potassium and water into the colon and are often used as a purging mechanism by patients with eating disorders (eg, bulimia nervosa) to prevent weight gain.

Unlike most other causes of diarrhea, which characteristically present with metabolic acidosis from loss of

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This patient's light-headedness, muscle cramps, and increased bathroom use are likely due to **diarrhea** caused by **laxative misuse**. Laxatives increase secretion of potassium and water into the colon and are often used as a purging mechanism by patients with eating disorders (eg, bulimia nervosa) to prevent weight gain.

Unlike most other causes of diarrhea, which characteristically present with metabolic acidosis from loss of bicarbonate in the stool, laxative misuse can also present with **metabolic alkalosis**:

- Chronic laxative misuse often produces more profound **hypokalemia** than other causes of diarrhea. The depleted potassium stimulates intracellular acidosis (transcellular shift: K^+ out of cells, H^+ into cells), resulting in increased ammonia and H^+ secretion by proximal and distal tubule cells, respectively. This leads to **increased bicarbonate generation** and resorption by the kidney.
- **Hypovolemia** and severe hypokalemia both increase activation of the renin-angiotensin-aldosterone system, with high levels of aldosterone stimulating further H^+ loss and bicarbonate generation by alpha-intercalated cells.

These 2 factors frequently **overcome the loss** of bicarbonate in the stool in patients with laxative-induced diarrhea, facilitating a net increase in serum bicarbonate.

(Choices A, C, D and E) Diarrhea due to laxative misuse can also sometimes present with metabolic acidosis or normal acid-base status. However, neither increased serum potassium nor decreased aldosterone levels would occur due to the loss of potassium and water in the stool.

Educational objective:
Laxative misuse increases secretion of potassium and water into the colon and can lead to profound hypokalemia and hypovolemia (with a compensatory increase in serum aldosterone). Metabolic alkalosis is a potential consequence, which contrasts with most other types of diarrhea that predominantly cause metabolic acidosis.

References

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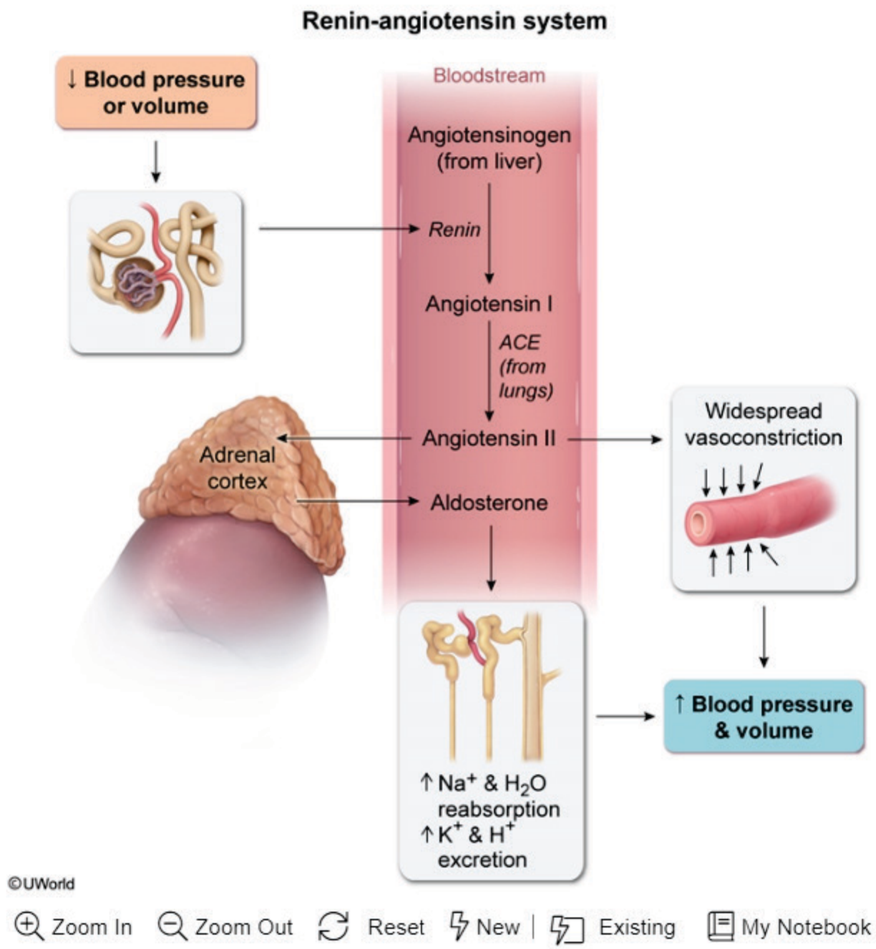
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This patient's light-headedness, muscle cramps, and increased bathroom use are likely due to **diarrhea** caused by **laxa**

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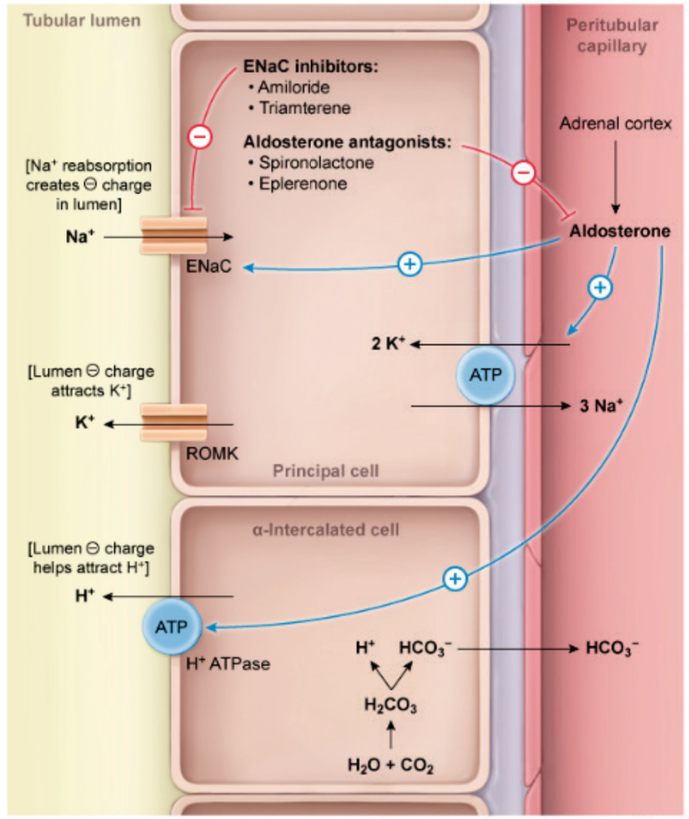
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References

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Action of aldosterone in the collecting duct of the nephron



ENaC = epithelial sodium channel; **ROMK** = renal outer medullary potassium channel. ©UWorld

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A 12-year-old girl is brought to the clinic by her parents after she is found to have hypertension by her school nurse. The patient has no symptoms and reads a book during the office visit. Her family immigrated to the United States 2 months ago, and she has not received routine well-child care. The patient has had several episodes of fever and abdominal pain, which her parents treated with over-the-counter antibiotics available in her country of origin. Blood pressure is elevated on several readings in the office. There is no family history of hypertension. Renal ultrasound reveals dilated calyces with overlying cortical atrophy bilaterally, mostly in the upper and lower poles. Which of the following is the most likely cause of this patient's condition?

- A. Autosomal dominant polycystic kidney disease
- B. Malignant hypertension
- C. Multicystic dysplastic kidneys
- D. Posterior urethral valves
- E. Reflux nephropathy

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- A. Autosomal dominant polycystic kidney disease (13%)
- ✕ B. Malignant hypertension (4%)
- C. Multicystic dysplastic kidneys (20%)
- D. Posterior urethral valves (17%)
- ✓ E. Reflux nephropathy (43%)

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Correct answer
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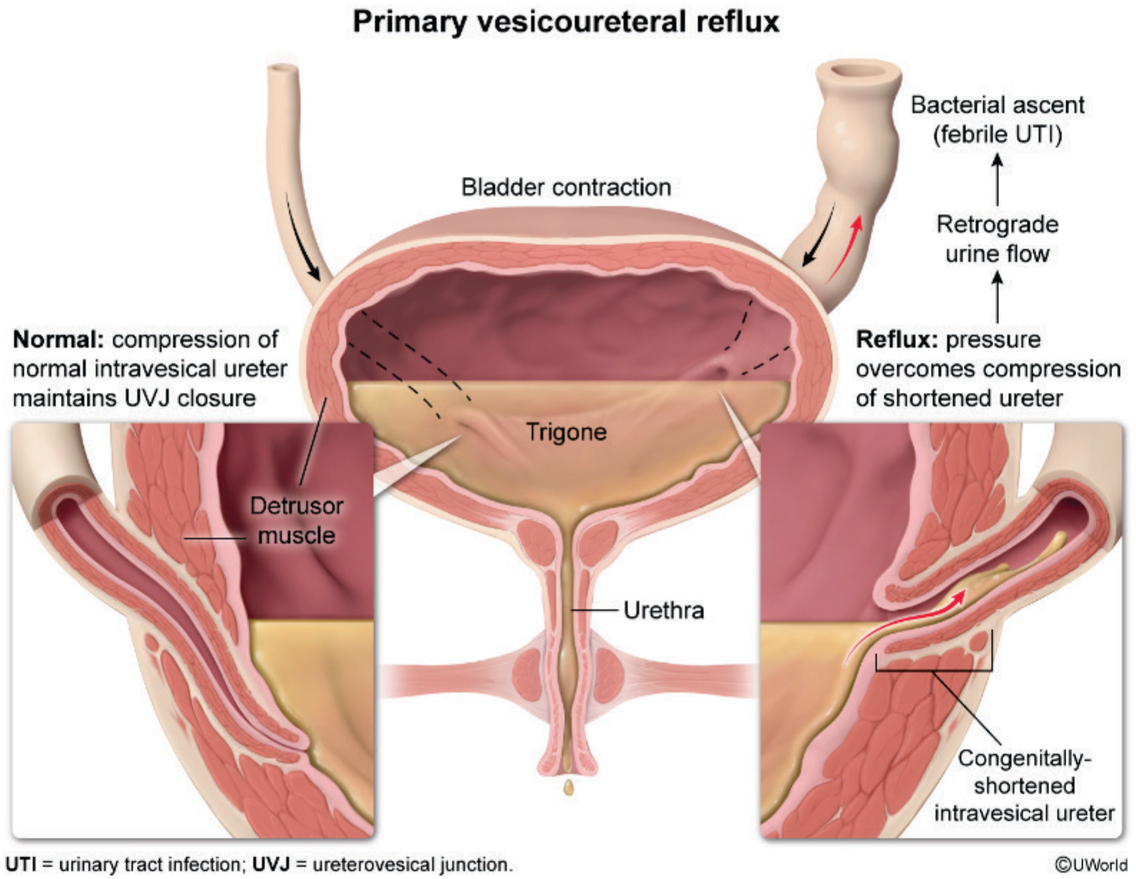
Explanation



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Primary vesicoureteral reflux

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ureter becomes compressed, and this flap-valve mechanism prevents retrograde flow of urine. However, this mechanism does not work correctly if the ureter enters the bladder wall at a more perpendicular angle, leading to

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This patient's history of recurrent fever and abdominal pain with imaging findings consistent with renal scarring (eg. dilated calyces with overlying cortical atrophy) is indicative of **recurrent pyelonephritis**. Pyelonephritis results from **retrograde flow** of bacteria in the bladder into the ureter, where they can then ascend unimpeded to the kidney.

Normally, the ureters travel through the bladder wall at an oblique angle. When the bladder fills, the intramural ureter becomes compressed, and this flap-valve mechanism prevents retrograde flow of urine. However, this mechanism does not work correctly if the ureter enters the bladder wall at a more perpendicular angle, leading to **vesicoureteral reflux** (VUR).

Patients with VUR are at much higher risk for chronic pyelonephritis. Renal inflammation can occur from pyelonephritis and also from VUR itself due to increased hydrostatic pressure on the papillae. Ongoing injury leads to **renal scarring**, most commonly at the upper and lower poles of the kidney in which compound papillae are found. Compound papillae are always open, unlike simple papillae in the mid-kidney, and are therefore more susceptible to dilation and subsequent injury. If uncorrected, chronic VUR can lead to reflux nephropathy and **secondary hypertension**.

(Choice A) Autosomal dominant polycystic kidney disease generally presents in adulthood with hematuria, hypertension, and renal insufficiency. Symptomatic patients have nephromegaly and diffuse parenchymal cysts on ultrasonography.

(Choice B) Malignant hypertension refers to very high blood pressure that develops rapidly and causes end-organ damage. Affected patients can have vision changes, encephalopathy, and renal failure. This patient has no evidence of acute end-organ dysfunction, and her imaging is more consistent with VUR and chronic pyelonephritis.

(Choice C) Multicystic dysplastic kidney (MCDK) is a nonhereditary renal malformation characterized by multiple noncommunicating cysts with intervening dysplastic tissue. Unilateral MCDK may be clinically silent, but bilateral MCDK presents with early, severe renal insufficiency due to the absence of functional renal tissue.

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vesicoureteral reflux (VUR).

Patients with VUR are at much higher risk for chronic pyelonephritis. Renal inflammation can occur from pyelonephritis and also from VUR itself due to increased hydrostatic pressure on the papillae. Ongoing injury leads to **renal scarring**, most commonly at the upper and lower poles of the kidney in which compound papillae are found. Compound papillae are always open, unlike simple papillae in the mid-kidney, and are therefore more susceptible to dilation and subsequent injury. If uncorrected, chronic VUR can lead to reflux nephropathy and **secondary hypertension**.

(Choice A) Autosomal dominant polycystic kidney disease generally presents in adulthood with hematuria, hypertension, and renal insufficiency. Symptomatic patients have nephromegaly and diffuse parenchymal cysts on ultrasonography.

(Choice B) Malignant hypertension refers to very high blood pressure that develops rapidly and causes end-organ damage. Affected patients can have vision changes, encephalopathy, and renal failure. This patient has no evidence of acute end-organ dysfunction, and her imaging is more consistent with VUR and chronic pyelonephritis.

(Choice C) Multicystic dysplastic kidney (MCDK) is a nonhereditary renal malformation characterized by multiple noncommunicating cysts with intervening dysplastic tissue. Unilateral MCDK may be clinically silent, but bilateral MCDK presents with early, severe renal insufficiency due to the absence of functional renal tissue.

(Choice D) Posterior urethral valves can present with bilateral hydronephrosis and calyceal dilation due to obstruction of urine flow in the urethra. However, posterior urethral valves result from a malformation of the wolffian duct and therefore only occur in male patients.

Educational objective:
Vesicoureteral reflux is characterized by retrograde urine flow from the bladder into the ureter. Affected patients are at increased risk of chronic pyelonephritis and subsequent renal scarring (eg. dilated calyces with overlying cortical atrophy).

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vesicoureteral reflux (VUR).

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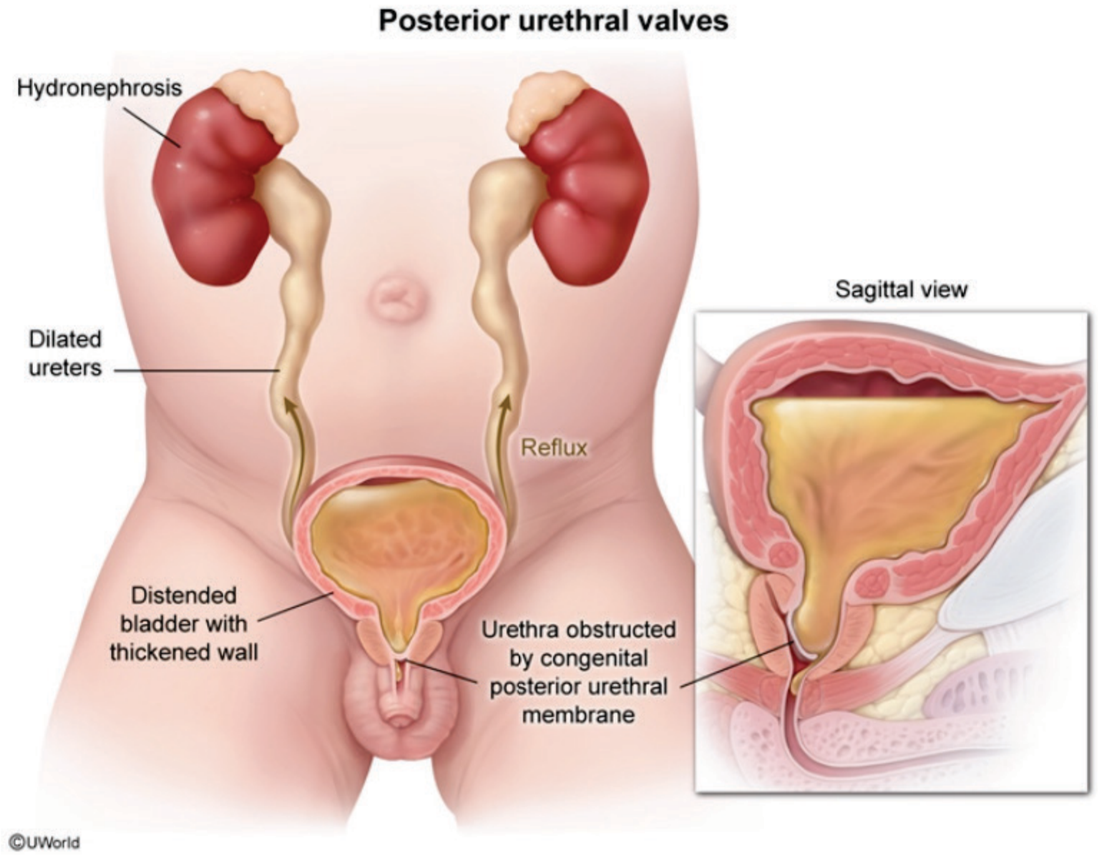
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A 42-year-old man comes to the office for evaluation of progressive generalized edema and weight gain for the past several weeks. He has no chest pain or shortness of breath. The patient has no chronic medical conditions and takes no medications. He last saw a physician a year ago for an upper respiratory infection. The patient does not use tobacco, alcohol, or illicit drugs. Blood pressure is 130/80 mm Hg and pulse is 84/min. Mild ascites is present. There is bilateral lower extremity pitting edema to the knees.

Laboratory results are as follows:

Serum chemistry	
Albumin	2.2 g/dL
Creatinine	1.0 mg/dL
Urinalysis	
Blood	negative
Protein	4+
Red blood cells	1-2/hpf
White blood cells	1-2/hpf

Urinary protein excretion is 6.0 g/24 hr. A kidney biopsy is performed, and electron microscopy of a glomerular capillary is shown below:

Which of the following is the most likely diagnosis?

- A. Crescentic glomerulonephritis
- B. Focal segmental glomerulosclerosis

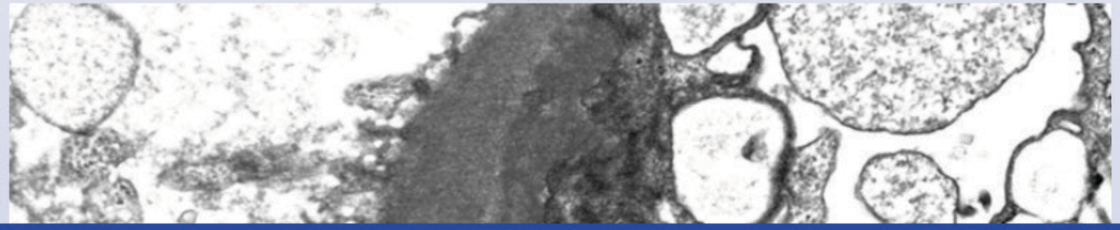
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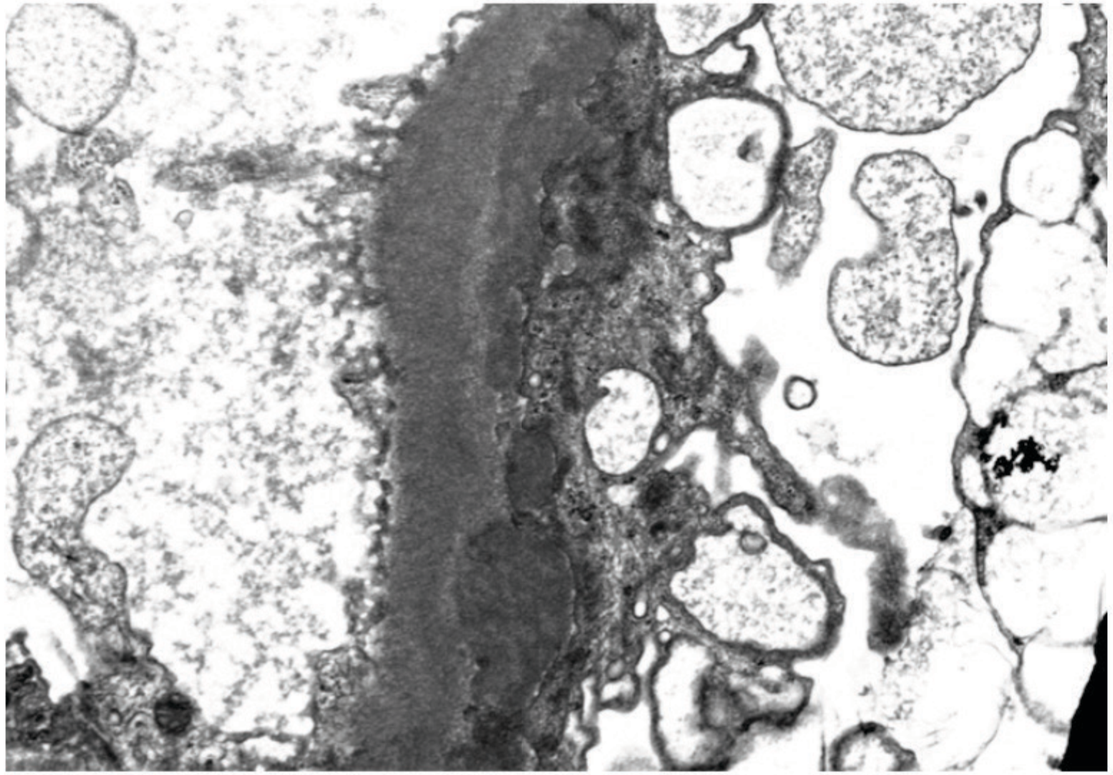


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Albumin 2.2 g/dL

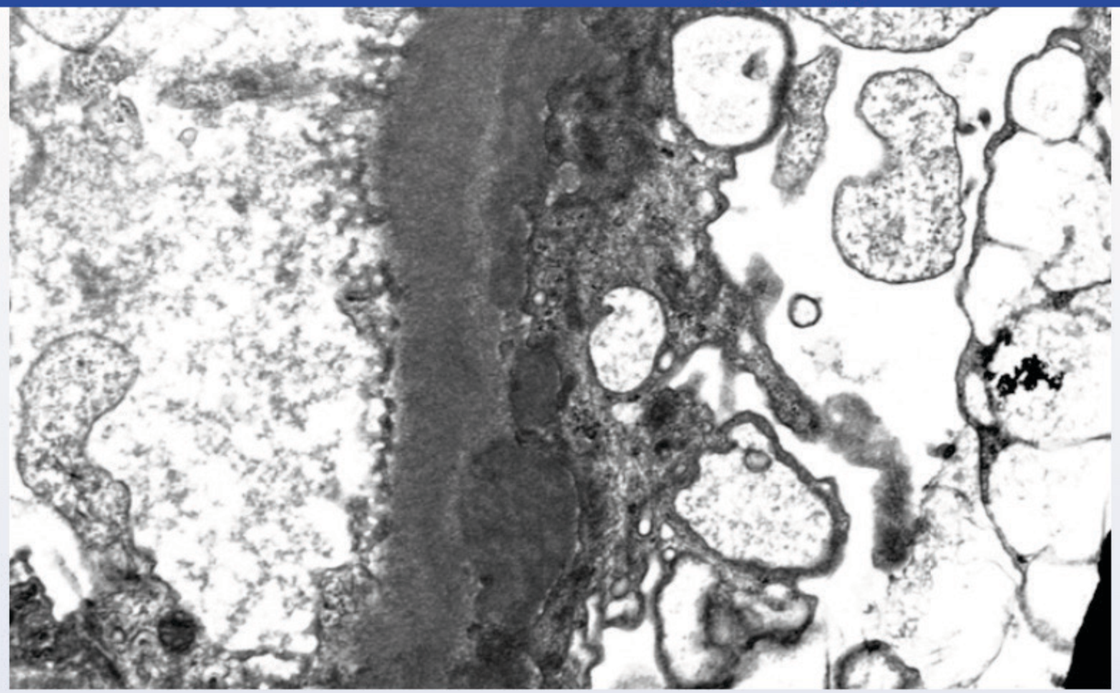
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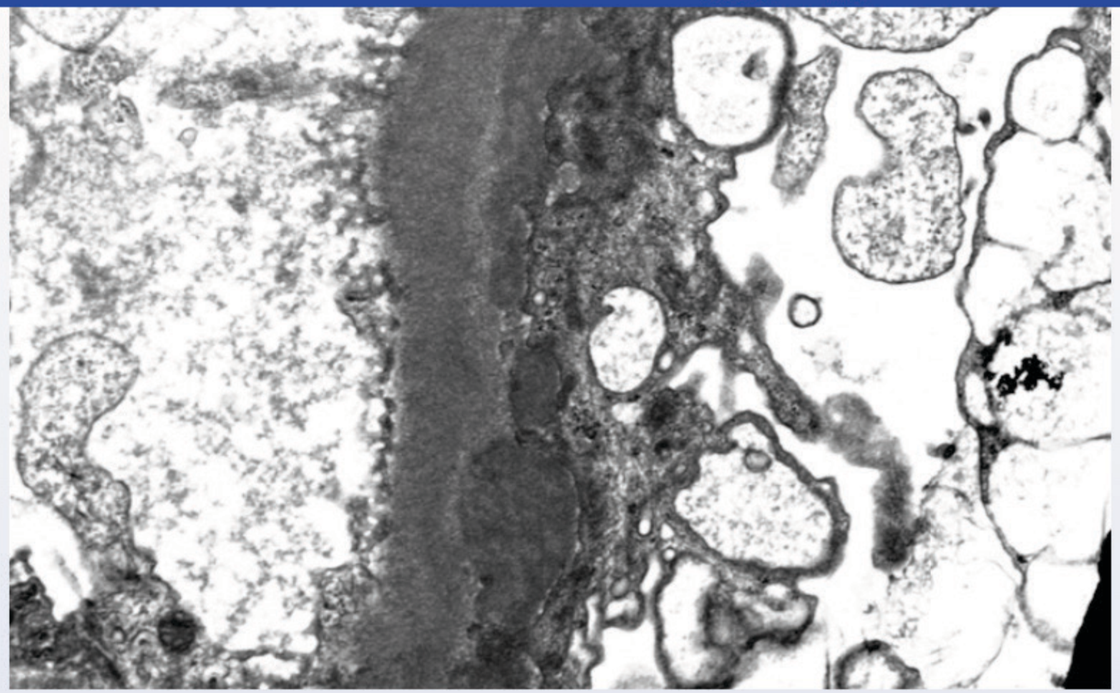


Which of the following is the most likely diagnosis?

- A. Crescentic glomerulonephritis
- B. Focal segmental glomerulosclerosis
- C. Membranous nephropathy
- D. Minimal change disease
- E. Poststreptococcal glomerulonephritis

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Which of the following is the most likely diagnosis?

- A. Crescentic glomerulonephritis (2%)
- ✗ B. Focal segmental glomerulosclerosis (11%)
- ✓ C. Membranous nephropathy (74%)
- D. Minimal change disease (5%)
- E. Poststreptococcal glomerulonephritis (5%)

Incorrect
Correct answer
C

74%
Answered correctly

14 secs
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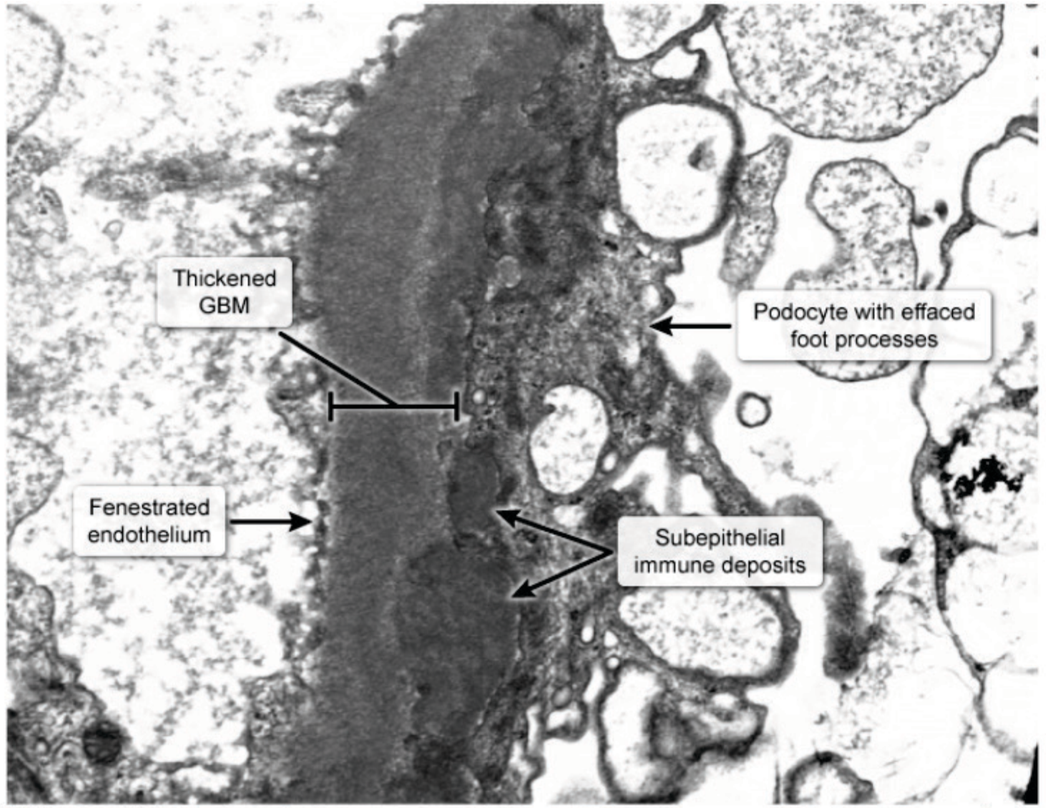
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E. Poststreptococcal glomerulonephritis (5%)

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Membranous nephropathy



GBM = glomerular basement membrane.

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GBM = glomerular basement membrane.

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This patient has **nephrotic syndrome**, characterized by generalized edema, heavy proteinuria (>3.5 g/day), and hypoalbuminemia. Electron microscopy (EM) of the glomerular capillary demonstrates irregular, electron-dense **immune deposits** located on the glomerular basement membrane (GBM) with moderate **effacement of the podocyte foot processes**, consistent with **membranous nephropathy** (MN). MN results from immune-complex deposition in the subepithelial portions of the GBM. Light microscopy demonstrates diffuse glomerular capillary wall thickening without hypercellularity, whereas silver staining reveals "**spikes and domes**" of GBM that protrude between the immune deposits (which do not stain). Immunofluorescence microscopy demonstrates a diffuse granular pattern of IgG and C3 along the capillary loops.

MN is one of the most common causes of nephrotic syndrome in adults. Primary (idiopathic) MN is thought to be caused by autoantibodies directed at the phospholipase A2 receptor, whereas secondary MN can be associated with a variety of conditions including systemic lupus erythematosus, viral hepatitis, and solid tumors.

(Choices A and E) Crescentic glomerulonephritis (GN) and poststreptococcal GN are nephritic diseases that are characterized by hematuria, red blood cell casts, and hypertension (not heavy proteinuria). Poststreptococcal GN typically occurs in children two to four weeks after a group A streptococcal infection, and EM demonstrates large, subepithelial immune-complex "humps." Crescentic (rapidly progressive) GN can occur in a number of diseases (eg, anti-GBM disease, antineutrophil cytoplasmic antibody vasculitis); proliferative crescents are visible on light microscopy, and EM may demonstrate rupture of the GBM.

(Choice B) Focal segmental glomerulosclerosis also causes nephrotic syndrome but is characterized by sclerosis and hyalinosis of portions of some, but not all, glomeruli. EM demonstrates diffuse foot process effacement; however, immune deposits (if present) typically occur in the sclerotic region of the glomerulus, not along the GBM.

(Choice D) Minimal change disease causes nephrotic syndrome but occurs more commonly in children. EM demonstrates extensive, diffuse effacement of the foot processes, and immune complexes are not seen.

Educational objective:

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wall thickening without hypercellularity, whereas silver staining reveals "**spikes and domes**" of GBM that protrude between the immune deposits (which do not stain). Immunofluorescence microscopy demonstrates a diffuse granular pattern of IgG and C3 along the capillary loops.

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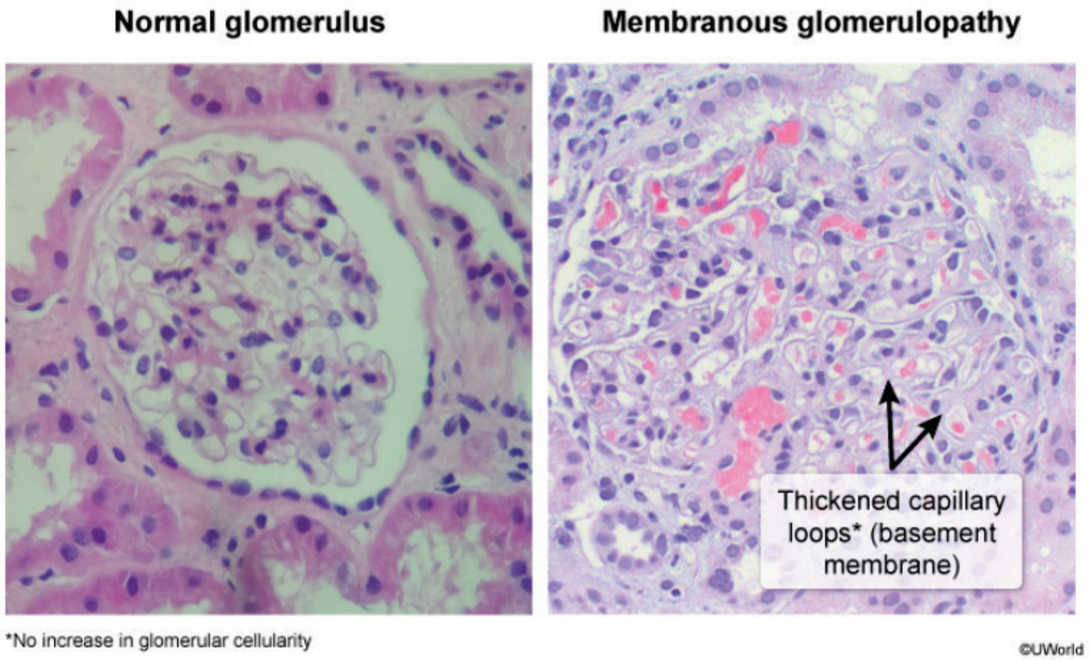
(Choice D) Minimal change disease causes nephrotic syndrome but occurs more commonly in children. EM demonstrates extensive, diffuse effacement of the foot processes, and immune complexes are not seen.

Educational objective:
Membranous nephropathy is a common cause of nephrotic syndrome in adults. Electron microscopy of the glomerular capillary demonstrates irregular, subepithelial, electron-dense immune deposits on the glomerular basement membrane with moderate effacement of the podocyte foot processes; immunofluorescence microscopy demonstrates a diffuse granular pattern of IgG along the capillary loops.

Pathology	Renal, Urinary Systems & Electrolytes	Membranous nephropathy
Subject	System	Topic

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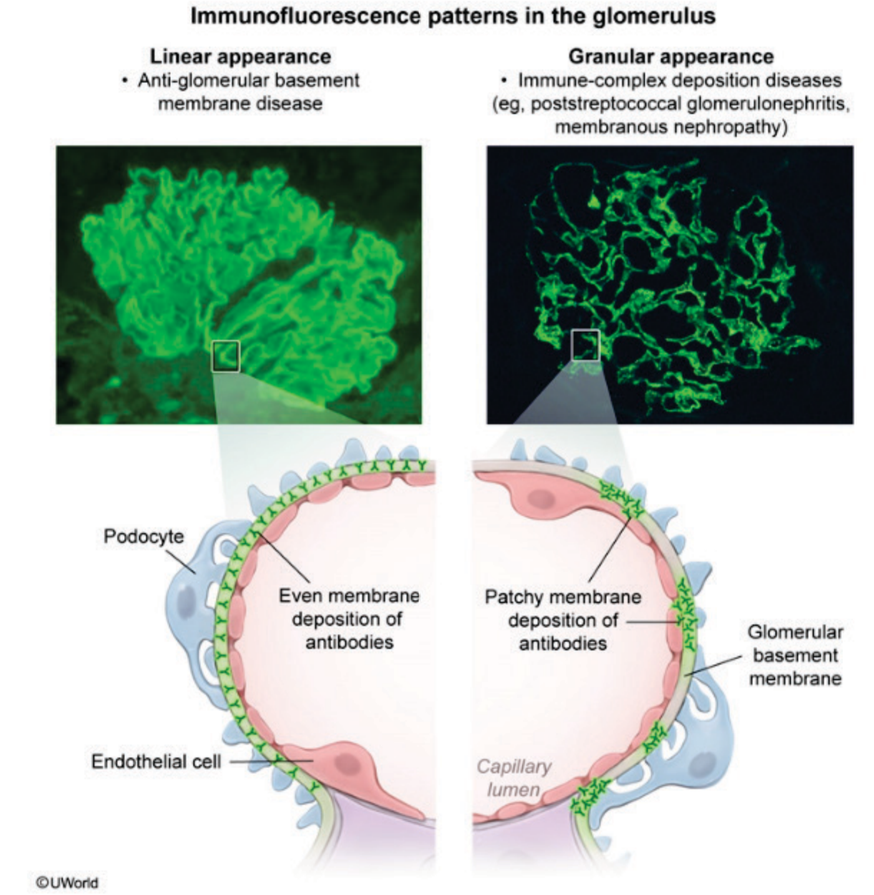
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however, immune deposits (if present) typically occur in the sclerotic region of the glomerulus, not along the GBM.

(Choice D) Minimal change disease causes nephrotic syndrome but occurs more commonly in children. FM

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however, immune deposits (if present) typically occur in the sclerotic region of the glomeruli, not along the GBM.

(Choice D) Minimal change disease causes nephrotic syndrome but occurs more commonly in children. FM

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GBM = glomerular basement membrane.

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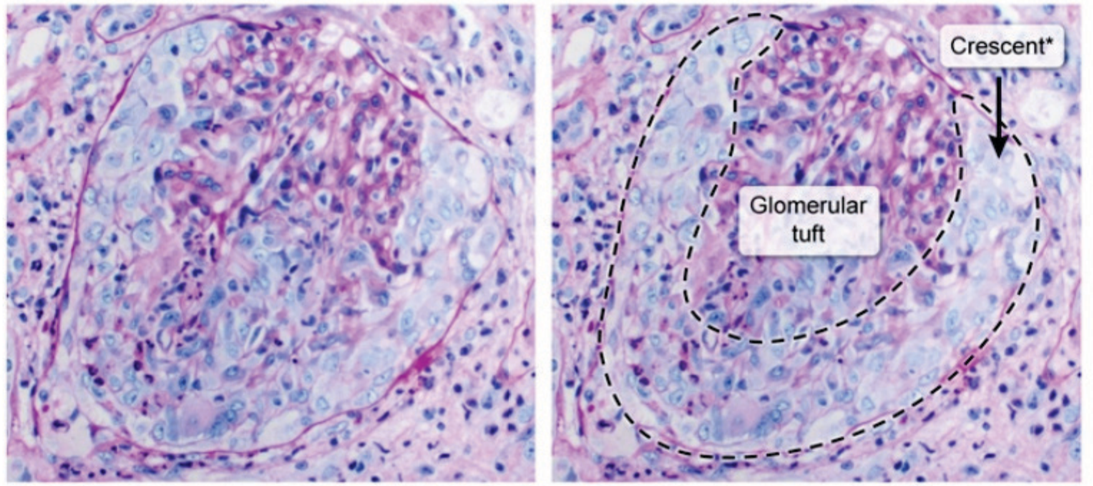
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Educational objective:

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Crescentic glomerulonephritis



*Proliferating epithelial cells and infiltrating macrophages

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GBM = glomerular basement membrane.

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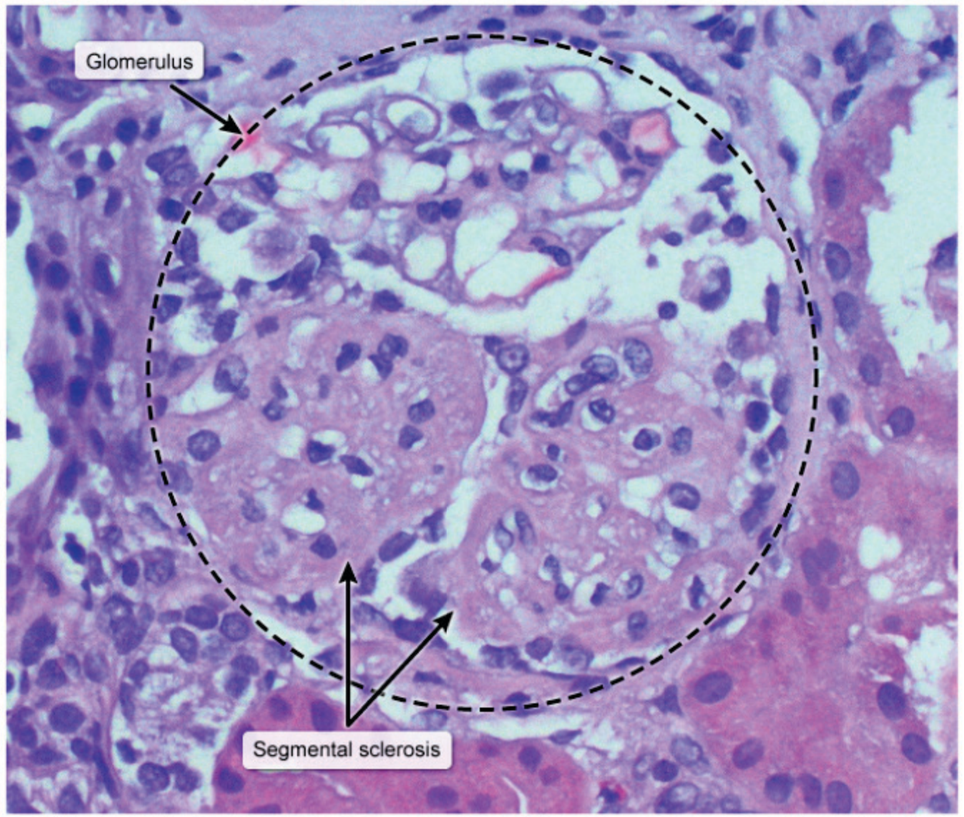
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Educational objective:

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Focal segmental glomerulosclerosis



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wall thickening without hypercellularity, whereas silver staining reveals "**spikes and domes**" of GBM that protrude

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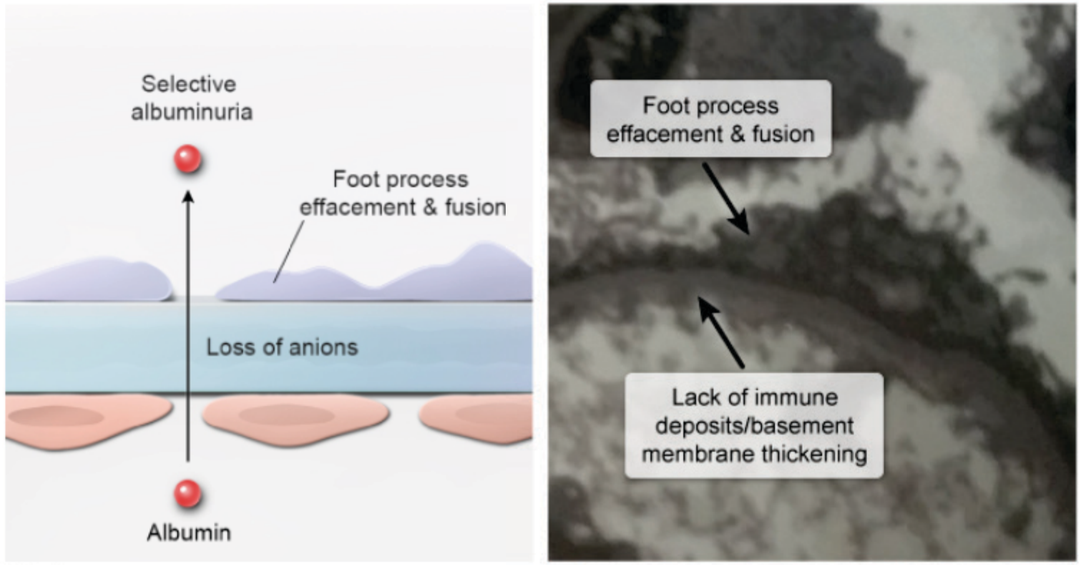
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Minimal change disease



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Pathology (Subject) | Renal, Urinary Systems & Electrolytes (System) | Membranous nephropathy (Topic)

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The following vignette applies to the next **2** items. The items in the set must be answered in sequential order. Once you click **Proceed to Next Item**, you will not be able to add or change an answer.

A 34-year-old man is brought to the emergency department with new-onset confusion and lethargy. Laboratory studies, including an arterial blood gas, are obtained. The changes in his blood gas parameters are shown in the graph below. Point A represents these parameters at the patient's physiologic baseline, and point B indicates his state on arrival in the emergency department.

Item 1 of 2

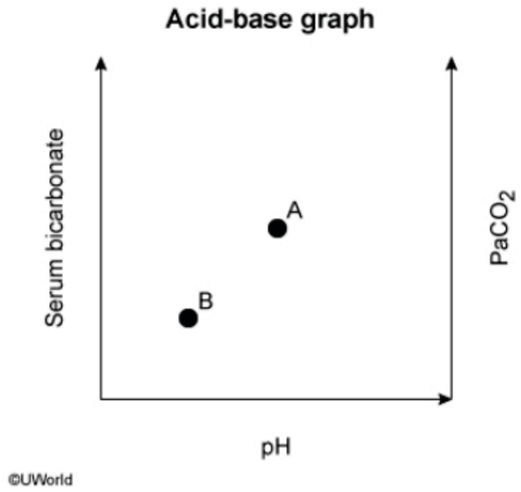
Which of the following is the most likely diagnosis?

- A. Metabolic acidosis
- B. Metabolic alkalosis
- C. Respiratory acidosis
- D. Respiratory alkalosis

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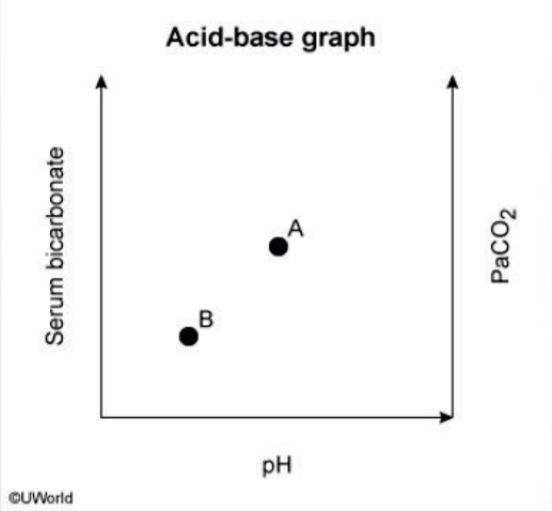
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C. Respiratory acidosis

studies, including an arterial blood gas, are obtained. The changes in his blood gas parameters are shown in the graph below. Point A represents these parameters at the patient's physiologic baseline, and point B indicates his state on arrival in the emergency department.



Item 1 of 2

Which of the following is the most likely diagnosis?

- A. Metabolic acidosis
- B. Metabolic alkalosis
- C. Respiratory acidosis
- D. Respiratory alkalosis

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Item 2 of 2

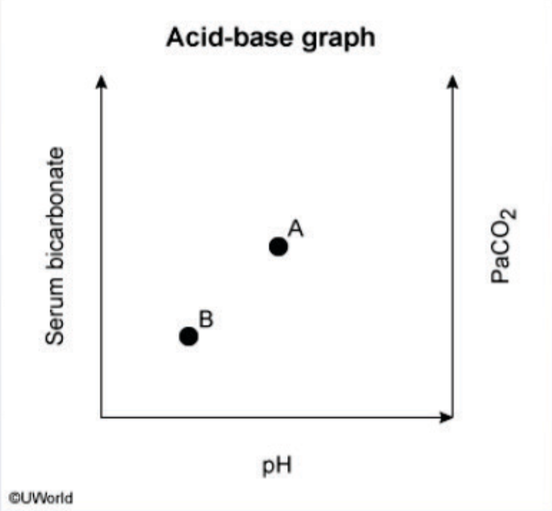
Results of the laboratory tests show an increased anion gap metabolic acidosis. An underlying cause is established, and appropriate treatment is instituted. Within several hours, the patient's mental status improves significantly. Repeat laboratory studies show an increase in serum bicarbonate and sodium levels, a decrease in serum osmolality, and a drop in the serum potassium level. Which of the following treatments was most likely given to this patient?

- A. Insulin and normal saline
- B. Loop diuretics
- C. Mineralocorticoid injection
- D. Opioid antagonists
- E. Thyroxine supplementation

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studies, including an arterial blood gas, are obtained. The changes in his blood gas parameters are shown in the graph below. Point A represents these parameters at the patient's physiologic baseline, and point B indicates his state on arrival in the emergency department.



Item 1 of 2

Which of the following is the most likely diagnosis?

- ✓ ○ A. Metabolic acidosis (91%)
- ✗ ◉ B. Metabolic alkalosis (3%)
- ○ C. Respiratory acidosis (3%)
- ○ D. Respiratory alkalosis (0%)

Incorrect
Correct answer
A

91%
Answered correctly

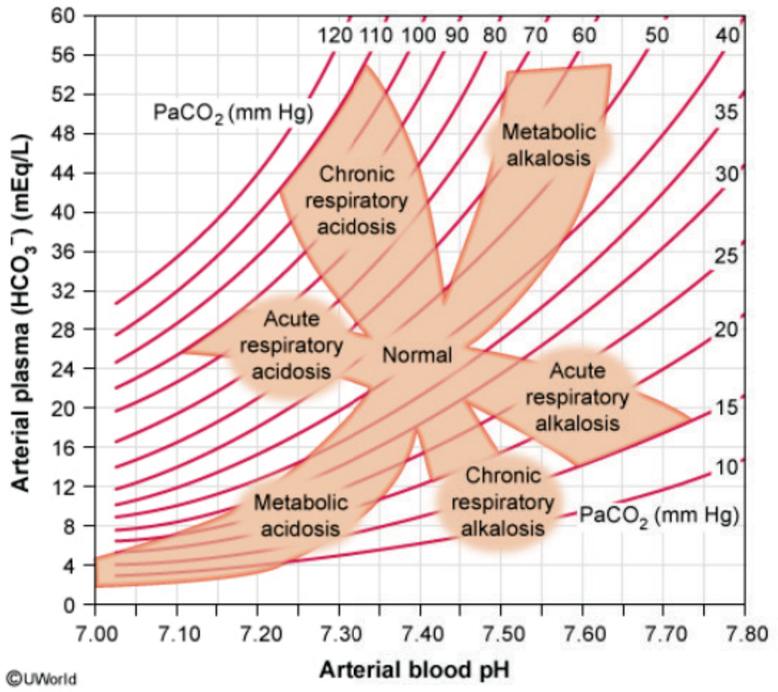
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D. Respiratory alkalosis (0%)

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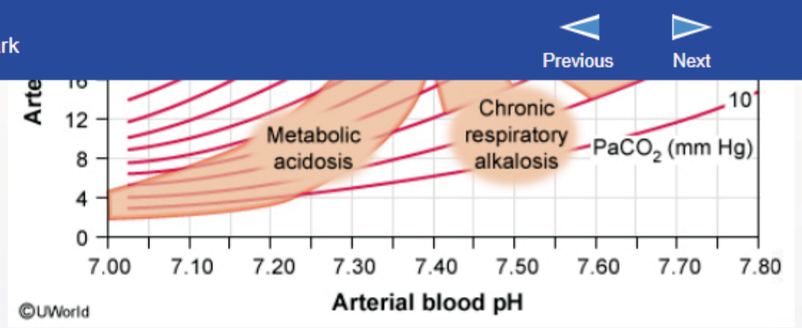


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state, which indicates **acidosis**. The next step is to determine whether the acidosis is driven by a metabolic or respiratory disturbance. Acidosis can be caused by either a decrease in serum bicarbonate (metabolic) or an

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Point B on the graph above shows that this patient has a **decreased pH** compared to his baseline physiologic state, which indicates **acidosis**. The next step is to determine whether the acidosis is driven by a metabolic or respiratory disturbance. Acidosis can be caused by either a decrease in serum bicarbonate (metabolic) or an increase in $PaCO_2$ (respiratory). This patient demonstrates **decreased serum bicarbonate**, indicating **metabolic acidosis** as the primary disturbance. The **decreased $PaCO_2$** represents **respiratory compensation** (via hyperventilation to breathe off CO_2) to help normalize the pH.

(Choice B) Metabolic alkalosis would be characterized by increased pH and serum bicarbonate. The $PaCO_2$ would also increase due to respiratory compensation.

(Choices C and D) Respiratory acidosis involves decreased pH and increased $PaCO_2$. Respiratory alkalosis is recognized by increased pH and decreased $PaCO_2$. Plasma bicarbonate gradually increases or decreases to compensate for the primary respiratory disturbance (renal compensation). However, unlike respiratory compensation, these responses are delayed and take place over ~72 hours.

Educational objective:
Metabolic acidosis is characterized by a decrease in serum pH and serum bicarbonate. $PaCO_2$ will also decrease due to respiratory compensation for the primary metabolic acidosis.

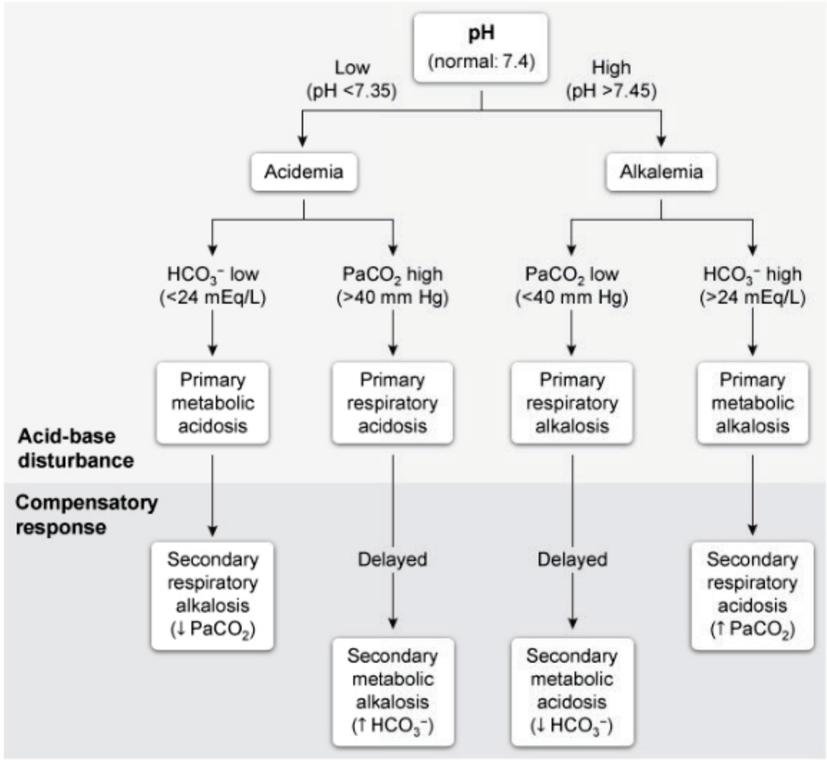
Pathology	Renal, Urinary Systems & Electrolytes	Diabetic ketoacidosis
Subject	System	Topic

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Arterial blood gas interpretation of acid-base disorders



* The normal ranges for $PaCO_2$ and HCO_3^- vary slightly around 40 mm Hg and 24 mEq/L.
For simplicity, these numbers should be used as a normal baseline for acid-base calculations.

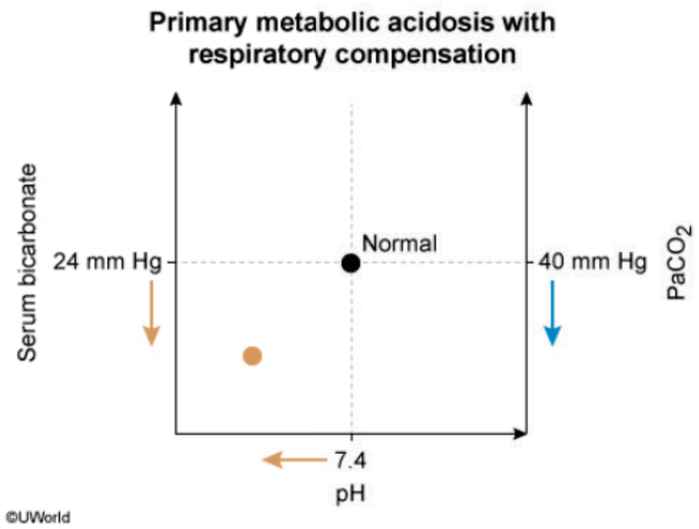
HCO_3^- = bicarbonate; **$PaCO_2$** = partial pressure of carbon dioxide in arterial blood.

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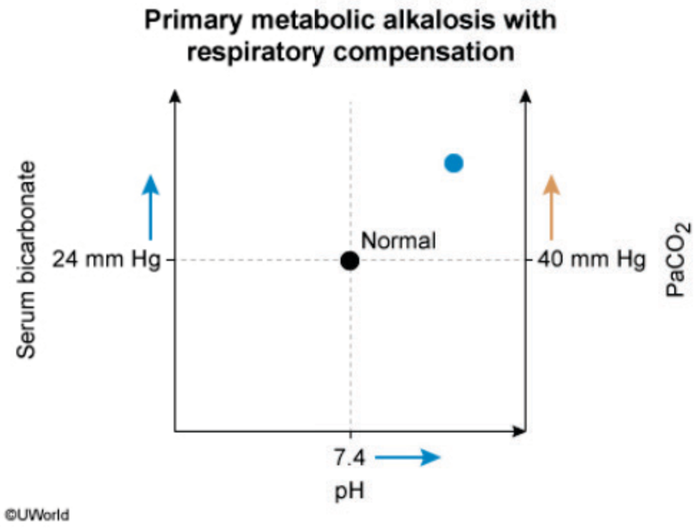
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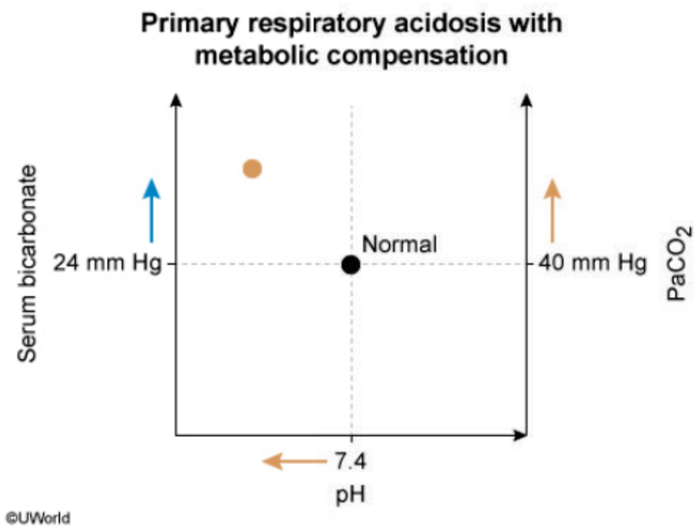
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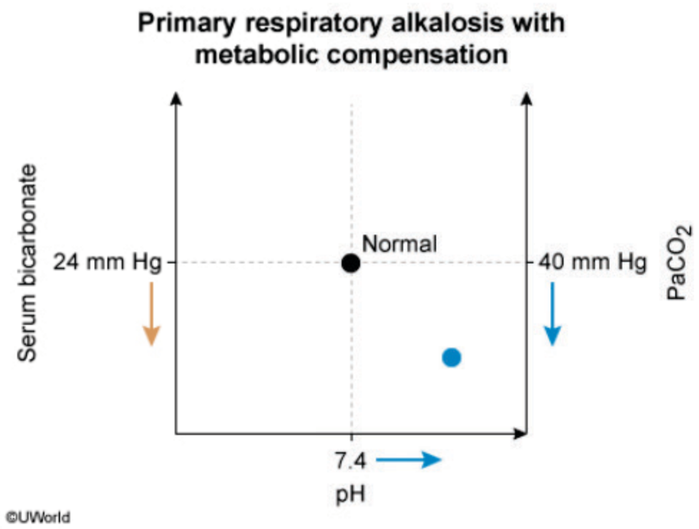
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Item 2 of 2

Results of the laboratory tests show an increased anion gap metabolic acidosis. An underlying cause is established, and appropriate treatment is instituted. Within several hours, the patient's mental status improves significantly. Repeat laboratory studies show an increase in serum bicarbonate and sodium levels, a decrease in serum osmolality, and a drop in the serum potassium level. Which of the following treatments was most likely given to this patient?

- ✓ A. Insulin and normal saline (67%)
- B. Loop diuretics (10%)
- ✗ C. Mineralocorticoid injection (20%)
- D. Opioid antagonists (0%)
- E. Thyroxine supplementation (0%)

Incorrect
Correct answer
A

67%
Answered correctly

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Explanation

Diabetic ketoacidosis

Lack of insulin

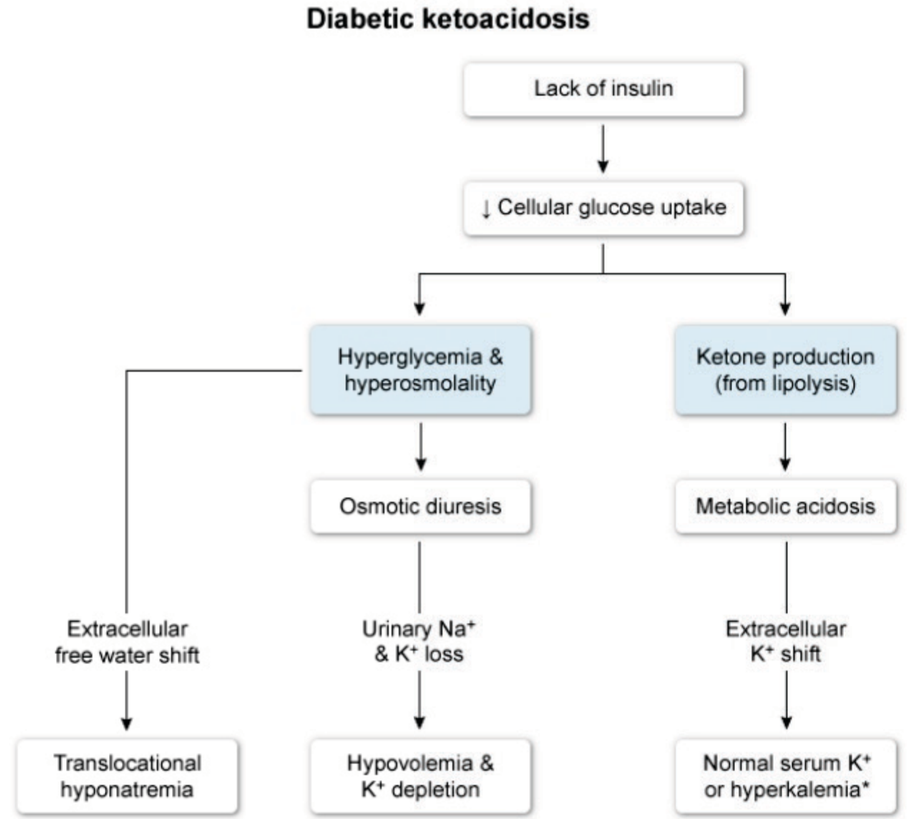
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↓ Cellular glucose uptake

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Explanation

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ketoacidosis (DKA). Patients classically have a fruity odor to the breath and often present with mental status

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This patient with an increased **anion gap metabolic acidosis** was most likely suffering from **diabetic ketoacidosis** (DKA). Patients classically have a fruity odor to the breath and often present with mental status changes, dehydration, abdominal pain, and tachypnea. Laboratory findings include **hyperglycemia**, ketosis, **mild hyponatremia**, normal or elevated serum potassium (despite a total body deficit), and **increased plasma osmolality**.

Insulin and hydration are the primary treatments for DKA. Insulin allows the cells to use glucose as an energy source, thereby decreasing lipolysis and production of ketone bodies. Because ketones are the principal acid produced in excess in patients with DKA, decreased production of ketone bodies will result in **increased serum bicarbonate**. Insulin also causes an intracellular shift of potassium, resulting in **decreased serum potassium** levels (patients typically require potassium repletion due to osmotic urinary loss). In addition to insulin-induced changes, rehydration with normal saline will help **normalize serum sodium** concentration (by providing isotonic sodium chloride) and decrease serum osmolality (by lowering serum glucose levels).

(Choice B) Loop diuretics could cause a decrease in potassium concentration as well as an increase in the serum concentration of bicarbonate. However, they also increase (not decrease) serum osmolality due to increased free water excretion (loop diuretics decrease the medullary concentration gradient, limiting the maximum tonicity of the urine).

(Choice C) Metabolic acidosis may develop in hypoaldosteronism (type 4 renal tubular acidosis), which is treated with exogenous mineralocorticoids. However, the combination of an increased anion gap and impaired mental status is not characteristic for hypoaldosteronism. Treatment with mineralocorticoids causes sodium and water retention with a mild increase (not decrease) in serum osmolality. Mineralocorticoids also decrease serum potassium and increase serum bicarbonate due to urinary K^+ and H^+ loss.

(Choice D) Opioid antagonists are useful in treating opioid overdoses, which typically cause respiratory acidosis (not anion gap metabolic acidosis) due to hypoventilation.

(Choice E) Thyroxine supplementation is useful in treating severe hypothyroidism, which may present with

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Insulin and hydration are the primary treatments for DKA. Insulin allows the cells to use glucose as an energy source, thereby decreasing lipolysis and production of ketone bodies. Because ketones are the principal acid produced in excess in patients with DKA, decreased production of ketone bodies will result in **increased serum bicarbonate**. Insulin also causes an intracellular shift of potassium, resulting in **decreased serum potassium** levels (patients typically require potassium repletion due to osmotic urinary loss). In addition to insulin-induced changes, rehydration with normal saline will help **normalize serum sodium** concentration (by providing isotonic sodium chloride) and decrease serum osmolality (by lowering serum glucose levels).

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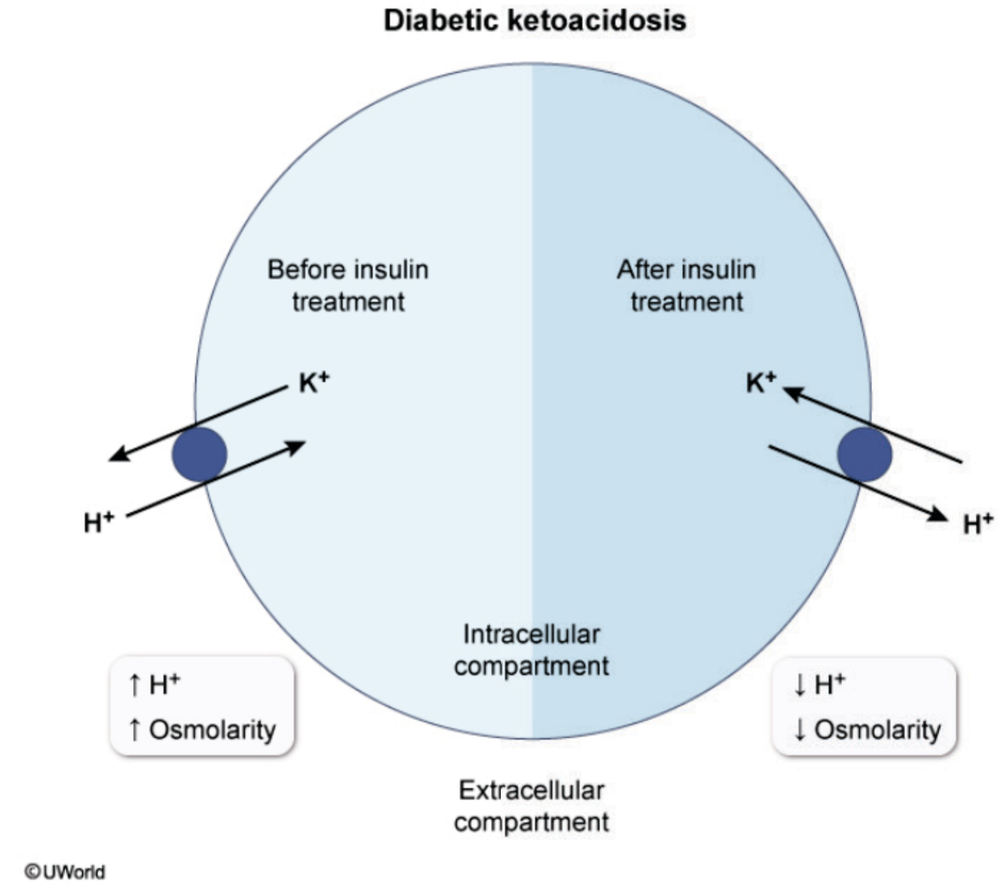
(Choice E) Thyroxine supplementation is useful in treating severe hypothyroidism, which may present with hyponatremia, extracellular volume expansion, and hypoglycemia.

Educational objective:
The treatment of choice for diabetic ketoacidosis is intravenous normal saline and insulin. These therapies increase serum bicarbonate and sodium levels, lower serum glucose and potassium levels, and decrease overall serum osmolarity.

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Translocational hyponatremia	Hypovolemia & K+ depletion	Normal serum K+ or hyperkalemia*

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potassium and increase serum bicarbonate due to urinary K^+ and H^+ loss.

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A 26-year-old previously healthy man comes to the office with a 3-week history of shortness of breath, cough, and hemoptysis preceded by an upper respiratory tract infection. He has no fever, night sweats, or weight loss. His blood pressure is 150/85 mm Hg and pulse is 86/min and regular. Physical examination reveals bilateral inspiratory crackles and lower extremity edema. His creatinine is 4.1 mg/dL. Urinalysis shows proteinuria and hematuria with dysmorphic red blood cells. Bilateral pulmonary infiltrates are seen on chest x-ray. He is also found to have an increased carbon monoxide diffusing capacity (DLCO) on pulmonary function testing. Antibodies directed against which of the following is most likely to be associated with this patient's condition?

- A. Alpha 3 chain of type IV collagen
- B. Beta-hemolytic streptococci
- C. Cardiolipin phospholipid
- D. Double-stranded DNA
- E. Topoisomerase I

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- ✓ A. Alpha 3 chain of type IV collagen (70%)
- ✗ B. Beta-hemolytic streptococci (16%)
- C. Cardiolipin phospholipid (6%)
- D. Double-stranded DNA (4%)
- E. Topoisomerase I (2%)

Incorrect
Correct answer
A

70%
Answered correctly

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Explanation

This patient has **Goodpasture syndrome**, which is caused by autoantibodies against the **alpha 3 chain of type IV collagen** found in the glomerular basement membrane (GBM) and pulmonary capillary membrane (**anti-GBM antibodies**). Antibody formation may be triggered by an antecedent viral respiratory infection, although most cases are idiopathic. These antibodies promote inflammatory injury of the glomerular and alveolar basement membranes, resulting in rapidly progressive glomerulonephritis and alveolar hemorrhage, respectively.

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This patient has **Goodpasture syndrome**, which is caused by autoantibodies against the **alpha 3 chain of type IV collagen** found in the glomerular basement membrane (GBM) and pulmonary capillary membrane (**anti-GBM antibodies**). Antibody formation may be triggered by an antecedent viral respiratory infection, although most cases are idiopathic. These antibodies promote inflammatory injury of the glomerular and alveolar basement membranes, resulting in rapidly progressive glomerulonephritis and alveolar hemorrhage, respectively.

Rapidly progressive glomerulonephritis results in nephritic syndrome, characterized by hypertension, edema, acute renal failure, hematuria (eg, dysmorphic red cells and red cell casts), and proteinuria. On renal biopsy, light microscopy shows glomerular crescent formation and immunofluorescence shows linear deposition of IgG and C3 on the GBM. **Alveolar hemorrhage** manifests with shortness of breath and hemoptysis with infiltrates on chest x-ray. Hemoglobin in the alveoli leads to increased alveolar oxygen absorption and high carbon monoxide diffusing capacity (DLCO).

(Choice B) Patients with beta-hemolytic streptococci infection of the pharynx or skin can develop glomerular immune complex deposition resulting in poststreptococcal glomerulonephritis and nephritic syndrome; however, this usually occurs in children and pulmonary involvement with alveolar hemorrhage is not characteristic.

(Choice C) Anticardiolipin antibodies are characteristic of antiphospholipid antibody syndrome, which typically presents with unprovoked/recurrent arterial and venous thrombosis or recurrent spontaneous abortions.

(Choice D) Antibodies to double-stranded DNA (dsDNA) are typically seen in systemic lupus erythematosus (SLE), particularly in individuals with active lupus nephritis. Although this patient has findings of glomerulonephritis, other features of SLE such as constitutional symptoms (eg, fatigue, fever, weight loss), malar rash, arthritis, serositis, and cytopenias are not evident. Pulmonary hemorrhage is also not characteristic of SLE.

(Choice E) Anti-topoisomerase I (anti-Scl-70) antibodies are found in patients with systemic sclerosis, which typically presents with diffuse thickening/hardening of the skin, Raynaud phenomenon, and esophageal dysfunction. Acute renal failure and hypertension may occur during scleroderma renal crisis; however, glomerulonephritis is not characteristic. Lung involvement typically leads to pulmonary fibrosis and pulmonary

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(Choice E) Anti-topoisomerase I (anti-Scl-70) antibodies are found in patients with systemic sclerosis, which typically presents with diffuse thickening/hardening of the skin, Raynaud phenomenon, and esophageal dysfunction. Acute renal failure and hypertension may occur during scleroderma renal crisis; however, glomerulonephritis is not characteristic. Lung involvement typically leads to pulmonary fibrosis and pulmonary arterial hypertension as opposed to pulmonary hemorrhage.

Educational objective:
Goodpasture syndrome is caused by autoantibodies against the alpha 3 chain of type IV collagen in glomerular and alveolar basement membranes (anti-GBM antibodies). Patients typically present with rapidly progressive glomerulonephritis (nephritic syndrome) and alveolar hemorrhage (shortness of breath, hemoptysis).

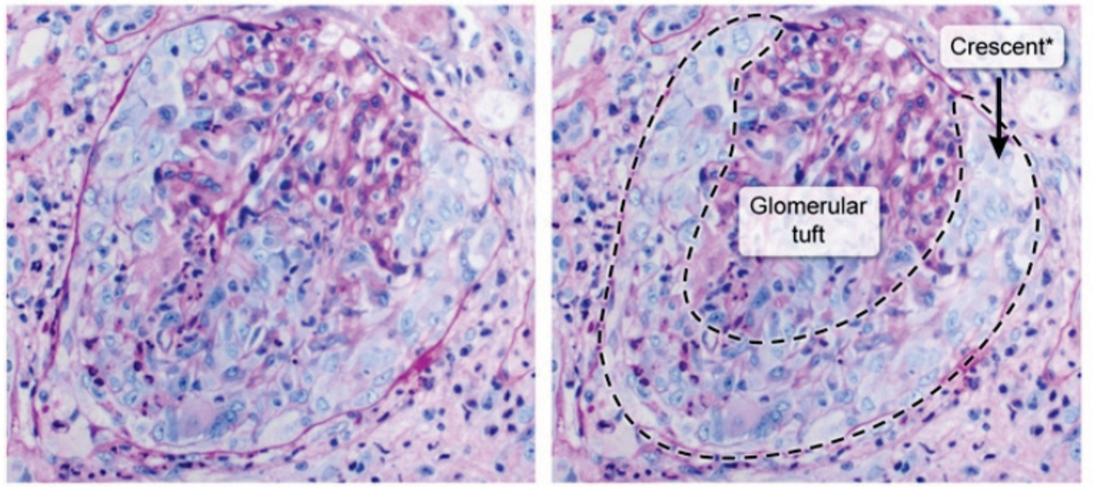
References

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Crescentic glomerulonephritis



*Proliferating epithelial cells and infiltrating macrophages

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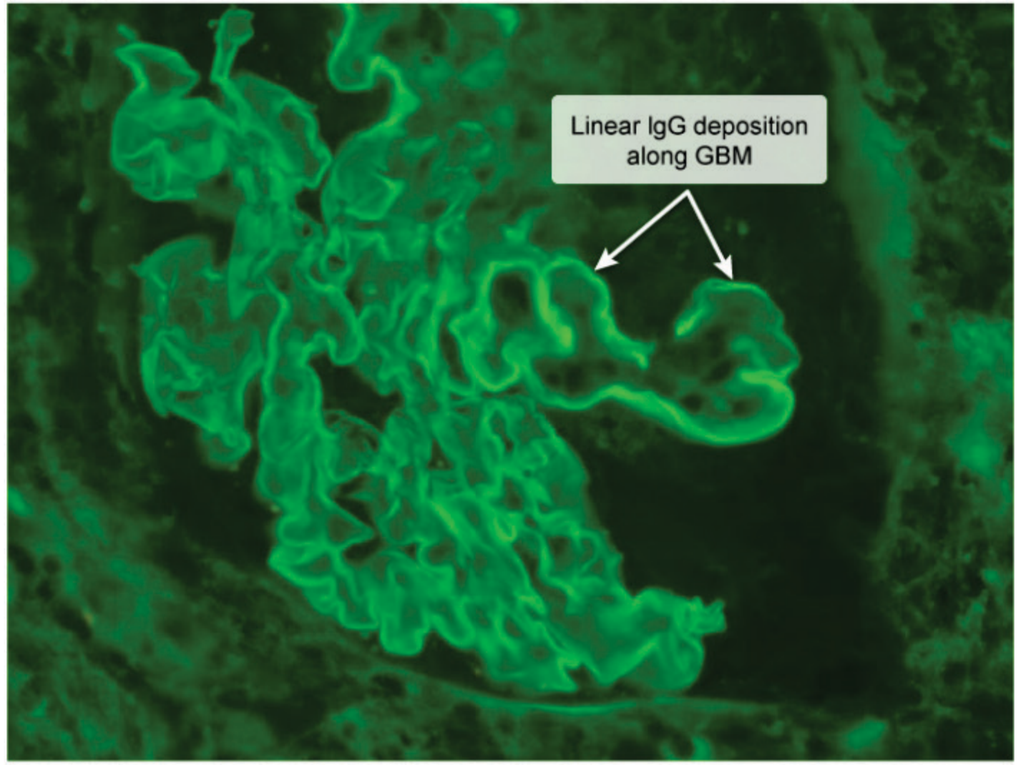
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(SLE), particularly in individuals with active lupus nephritis. Although this patient has findings of glomerulonephritis, other features of SLE such as constitutional symptoms (eg, fatigue, fever, weight loss), malar

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Anti–glomerular basement membrane disease (Goodpasture syndrome)



Immunofluorescence

GBM = glomerular basement membrane.

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An experimental substance is infused intravenously at a constant rate into a healthy volunteer. The substance is known to selectively constrict the efferent arteriole in renal glomeruli. The rate of infusion is closely controlled during the experiment to allow for only mild constriction of the efferent arteriole. Which of the following changes in glomerular filtration rate (GFR) and filtration fraction (FF) is most likely to occur during the infusion of this substance?

- A. GFR↓, FF↑
- B. GFR↓, FF unchanged
- C. GFR↑, FF↓
- D. GFR↑, FF↑
- E. GFR unchanged, FF↑

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An experimental substance is infused intravenously at a constant rate into a healthy volunteer. The substance is known to selectively constrict the efferent arteriole in renal glomeruli. The rate of infusion is closely controlled during the experiment to allow for only mild constriction of the efferent arteriole. Which of the following changes in glomerular filtration rate (GFR) and filtration fraction (FF) is most likely to occur during the infusion of this substance?

- A. GFR↓, FF↑ (7%)
- ✗ B. GFR↓, FF unchanged (4%)
- C. GFR↑, FF↓ (6%)
- ✓ D. GFR↑, FF↑ (77%)
- E. GFR unchanged, FF↑ (3%)

Incorrect
Correct answer
D

77%
Answered correctly

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Time Spent

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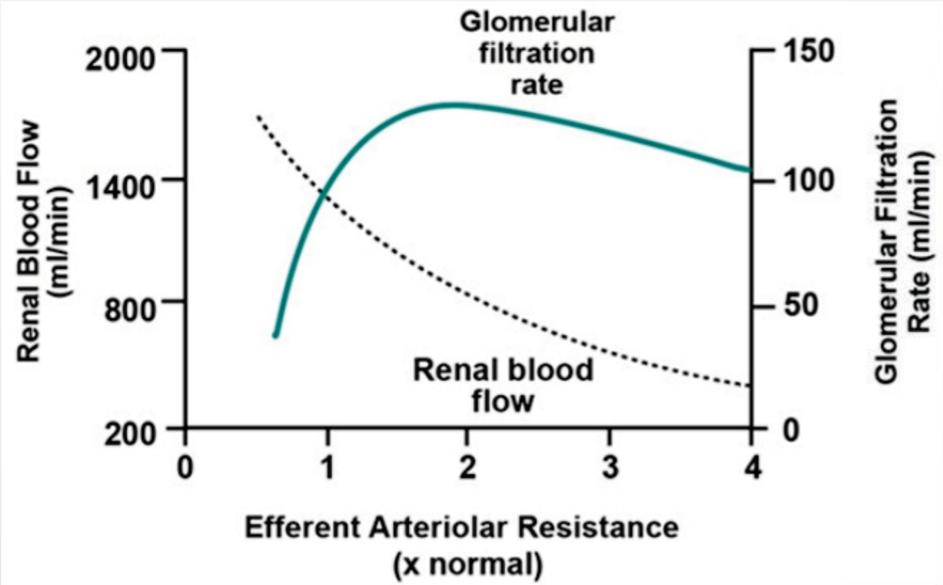
Explanation

Blood circulates in the kidney along the following path: interlobar arteries→arcuate arteries→radial arteries→afferent arterioles→glomerular capillaries→efferent arterioles→peritubular capillaries→interlobar veins. Glomerular filtration rate (GFR) normally equals approximately 125 ml/min, although this number can vary between 90 to 130 by gender and between different subjects. The GFR depends on the difference in hydrostatic and oncotic pressures between the glomerular capillaries and Bowman's capsule.



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Constriction of the efferent arteriole produces a significant increase in glomerular capillary hydrostatic pressure because of the reduction in glomerular blood outflow. This produces a corresponding increase in GFR. Efferent arteriolar constriction also reduces renal plasma flow (RPF). The increase in GFR along with the decrease in RPF leads to an increased filtration fraction (FF) because FF=GFR/RPF (**Choice D**).

As RPF decreases, the slower capillary flow allows more time for the filtration of plasma across the glomerular membrane. This leads to an increased concentration of non-filterable plasma proteins within the glomerular capillaries, thus elevating capillary oncotic pressure. As efferent arteriolar constriction increases past a certain

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(x normal)

Constriction of the efferent arteriole produces a significant increase in glomerular capillary hydrostatic pressure because of the reduction in glomerular blood outflow. This produces a corresponding increase in GFR. Efferent arteriolar constriction also reduces renal plasma flow (RPF). The increase in GFR along with the decrease in RPF leads to an increased filtration fraction (FF) because FF=GFR/RPF (**Choice D**).

As RPF decreases, the slower capillary flow allows more time for the filtration of plasma across the glomerular membrane. This leads to an increased concentration of non-filterable plasma proteins within the glomerular capillaries, thus elevating capillary oncotic pressure. As efferent arteriolar constriction increases past a certain point, this increase in capillary oncotic pressure begins to oppose, and eventually overwhelm, the increase in capillary hydrostatic pressure also produced by efferent arteriolar constriction. Thus, when RPF is low secondary to severe efferent arteriolar constriction, the substantially increased capillary oncotic pressure results in an overall decrease in GFR **(Choice A)**.

(Choice B) Selective constriction of the afferent arteriole decreases plasma flow into the glomerular capillaries, reducing capillary hydrostatic pressure and thus decreasing the GFR. Constriction of the afferent arteriole results in relatively equal decreases in RPF and GFR (FF=GFR/RPF), so the filtration fraction remains unchanged.

Educational objective:
Selective vasoconstriction of the efferent arteriole (up to certain extent) increases hydrostatic pressure in the glomerular capillaries, and therefore increases the glomerular filtration rate. As efferent arteriolar constriction continues to increase, the glomerular filtration rate begins to decrease due to a flow-mediated rise in oncotic pressure in the glomerular capillaries. The filtration fraction always increases with increasing efferent arteriole constriction.

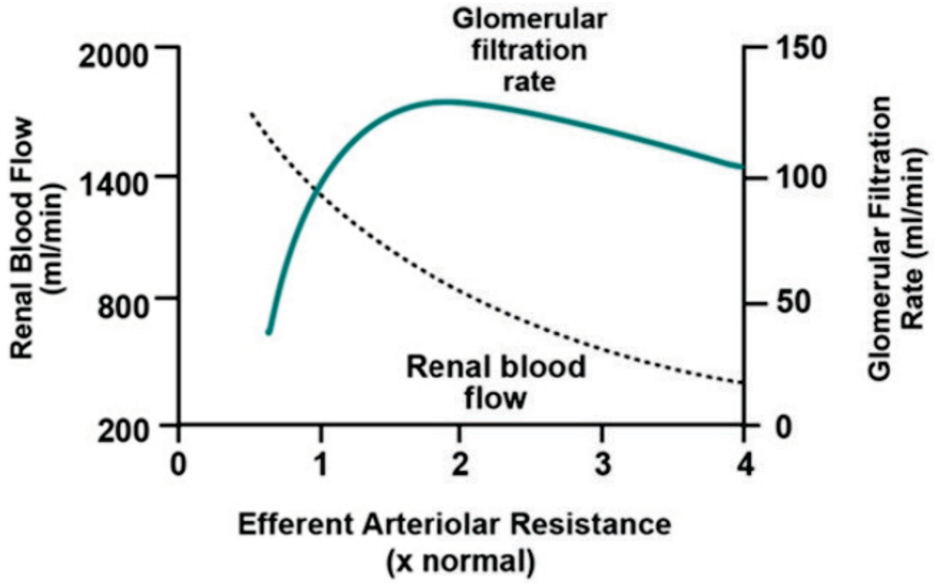
Physiology	Renal, Urinary Systems & Electrolytes	GFR
Subject	System	Topic

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Glomerular

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(Choice B) Selective constriction of the afferent arteriole decreases plasma flow into the glomerular capillaries,

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A 56-year-old woman with polycystic kidney disease comes to the office for follow up. Her renal function has been gradually declining, and she is being considered for hemodialysis in the near future. The patient has recently experienced increasing exertional dyspnea and fatigue but has had no fever, dysuria, or flank pain. Other medical conditions include hypertension and renal calculi. Blood pressure is 130/86 mm Hg and pulse is 80/min. Physical examination shows mucosal pallor. The lungs are clear on auscultation and heart sounds are normal. Abdominal examination reveals palpably enlarged kidneys. There is no lower extremity edema. Laboratory results show normocytic, normochromic anemia, which is attributed to insufficient hormone production by the kidneys. This hormone is predominantly secreted by which of the following parts of the kidney?

- A. Efferent arteriolar smooth muscles
- B. Glomerular podocytes
- C. Juxtaglomerular cells
- D. Peritubular interstitial cells
- E. Proximal tubule epithelium

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- A. Efferent arteriolar smooth muscles (3%)
- ✗ B. Glomerular podocytes (0%)
- C. Juxtaglomerular cells (17%)
- ✓ D. Peritubular interstitial cells (66%)
- E. Proximal tubule epithelium (11%)

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Correct answer
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66%
Answered correctly

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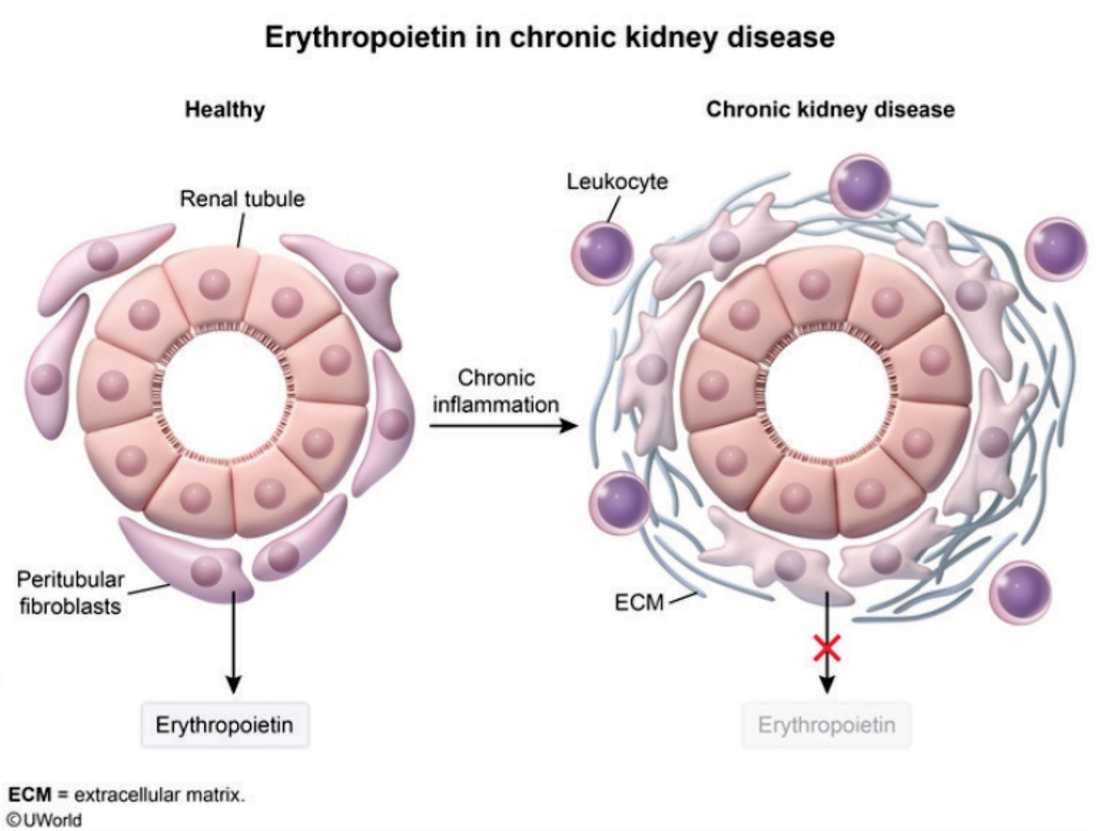
Explanation

Erythropoietin in chronic kidney disease

Healthy

Chronic kidney disease

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Patients with **chronic kidney disease** (CKD) often develop symptomatic anemia (eg, fatigue, exertional dyspnea) as the glomerular filtration rate declines. Most cases are due to the **inadequate secretion of erythropoietin** (EPO), a glycoprotein hormone produced by **peritubular fibroblasts in the renal cortex** in response to tissue hypoxia (as is seen with anemia). EPO acts on erythrocyte precursor cells (erythroid colony–forming unit cells) in the bone marrow to stimulate red blood cell differentiation and survival.

Healthy patients increase EPO levels up to 10,000-fold in response to anemia, but patients with CKD have chronic inflammatory damage to renal EPO-producing cells and are often unable to generate sufficient EPO to maintain red

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Healthy patients increase EPO levels up to 10,000-fold in response to anemia, but patients with CKD have chronic inflammatory damage to renal EPO-producing cells and are often unable to generate sufficient EPO to maintain red blood cell counts. These individuals are often treated with **synthetic EPO agents** (eg, epoetin, darbepoetin) to stimulate erythrocyte production. As iron is rapidly consumed to make red blood cells, individuals treated with EPO agents are often also given iron supplementation to prevent the development of iron deficiency anemia.

In adults, approximately 80% of EPO is generated in the kidney; the remainder is largely generated in the liver by hepatocytes and Ito perisinusoidal cells.

(Choices A and C) Decreased renal perfusion and glomerular filtration leads to decreased solute delivery to the juxtaglomerular apparatus in the distal tubule, which stimulates renin secretion by juxtaglomerular cells. Activation of the renin-angiotensin-aldosterone system leads to increased production of angiotensin II, a potent vasoconstrictor that preferentially constricts the efferent arteriole to restore glomerular filtration. These hormones do not have a substantial effect on red cell production.

(Choices B and E) Foot processes of renal podocytes surround glomerular capillaries to prevent filtration of large molecules (eg, plasma proteins); defects can cause chronic proteinuric kidney disease (eg, minimal change disease). Epithelial cells of the proximal tubule have a prominent role in reabsorption and secretion of solutes into the urine; these cells have high metabolic activity and are therefore susceptible to ischemic injury (eg, acute tubular necrosis) due to inadequate renal perfusion and oxygen delivery. However, neither of these cell types produces EPO.

Educational objective:

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Healthy patients increase EPO levels up to 10,000-fold in response to anemia, but patients with CKD have chronic inflammatory damage to renal EPO-producing cells and are often unable to generate sufficient EPO to maintain red blood cell counts. These individuals are often treated with **synthetic EPO agents** (eg, epoetin, darbepoetin) to stimulate erythrocyte production. As iron is rapidly consumed to make red blood cells, individuals treated with EPO agents are often also given iron supplementation to prevent the development of iron deficiency anemia.

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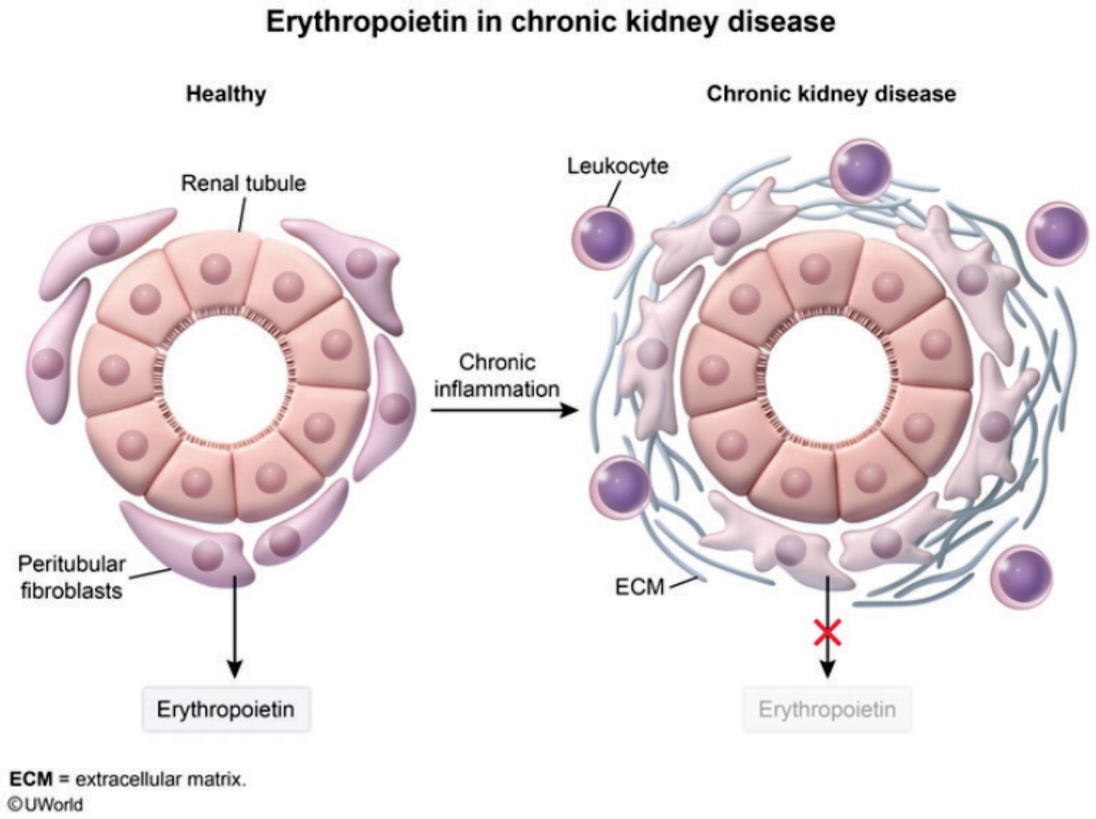
Educational objective:
Erythropoietin (EPO) is produced primarily by peritubular fibroblast cells in the renal cortex in response to decreased renal oxygen delivery (eg, decreased blood hemoglobin content). EPO acts on erythrocyte precursor cells in the bone marrow to stimulate red blood cell production. Patients with chronic kidney disease have inflammatory damage to renal EPO-producing cells and often develop normocytic anemia due to insufficient EPO.

References

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inflammation

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ECM = extracellular matrix.
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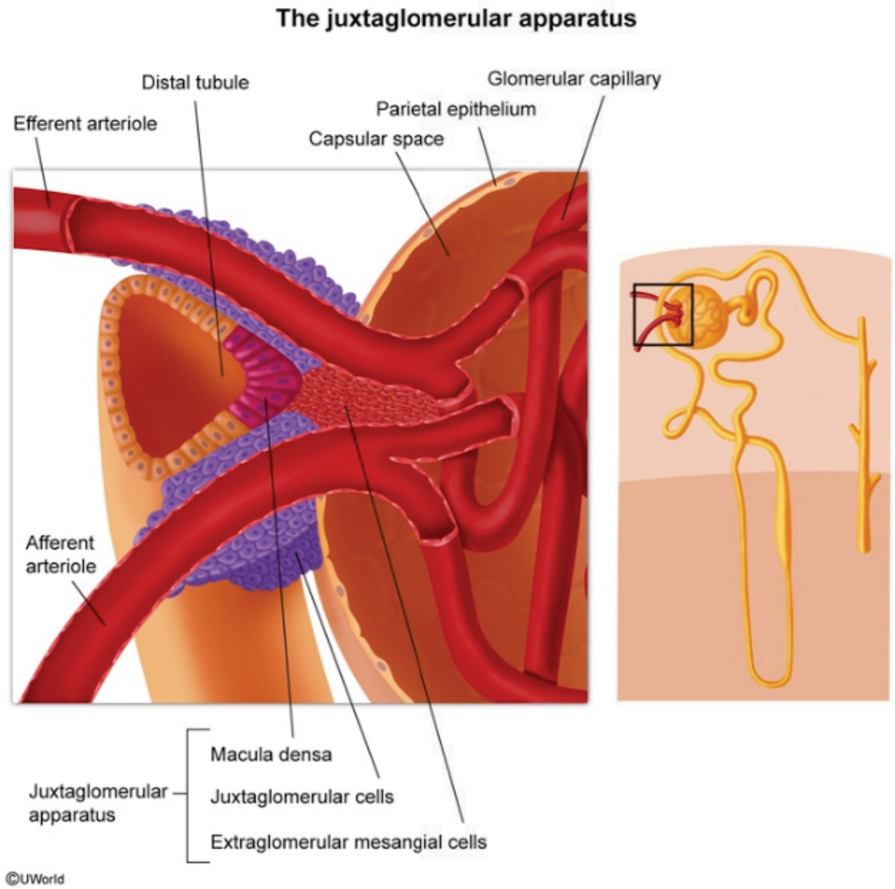
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Educational objective:

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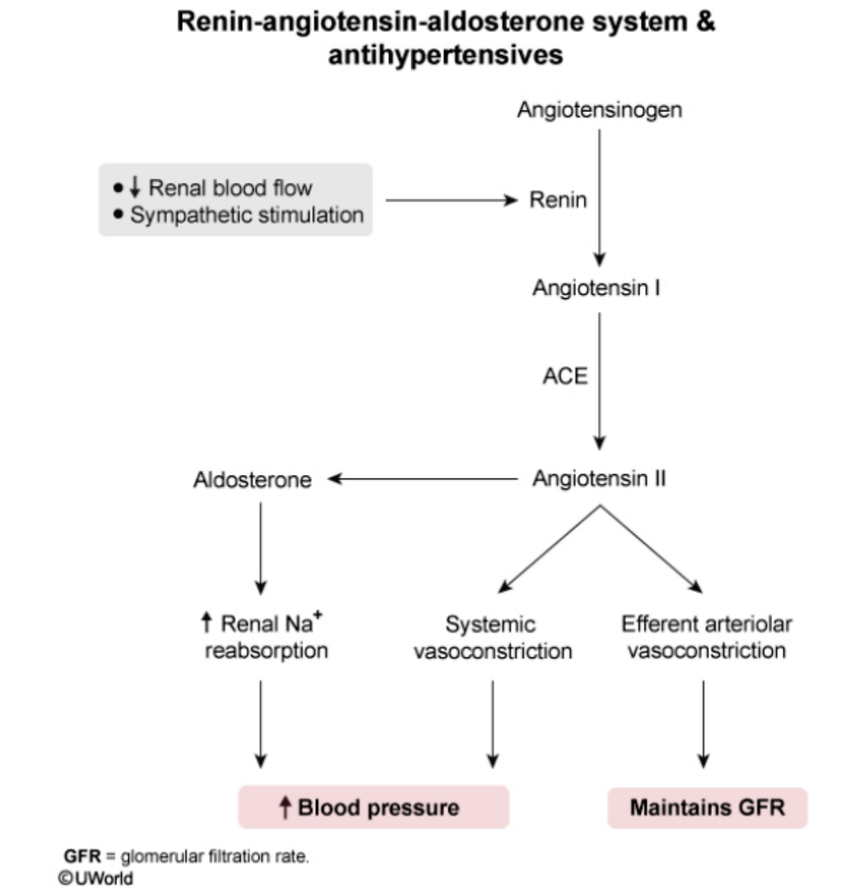
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A 54-year-old man hospitalized with an acute myocardial infarction goes into cardiac arrest. The patient is resuscitated successfully and transferred to the cardiac intensive care unit where he remains hemodynamically stable. However, on the second day of hospitalization, his urine flow diminishes to 400 mL/day. Blood pressure is 115/68 mm Hg and pulse is 78/min. Laboratory results are as follows:

	Day 1	Day 2
Sodium	134 mEq/L	133 mEq/L
Potassium	4.2 mEq/L	4.0 mEq/L
Chloride	96 mEq/L	94 mEq/L
Bicarbonate	26 mEq/L	22 mEq/L
Blood urea nitrogen	16 mg/dL	26 mg/dL
Creatinine	1.1 mg/dL	2.4 mg/dL

Urine sediment microscopy reveals muddy brown casts. Which of the following renal structures are most likely to demonstrate signs of ischemic injury?

- A. Collecting ducts
- B. Distal tubules
- C. Glomeruli
- D. Proximal tubules
- E. Renal papillae

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A 54-year-old man hospitalized with an acute myocardial infarction goes into cardiac arrest. The patient is resuscitated successfully and transferred to the cardiac intensive care unit where he remains hemodynamically stable. However, on the second day of hospitalization, his urine flow diminishes to 400 mL/day. Blood pressure is 115/68 mm Hg and pulse is 78/min. Laboratory results are as follows:

	Day 1	Day 2
Sodium	134 mEq/L	133 mEq/L
Potassium	4.2 mEq/L	4.0 mEq/L
Chloride	96 mEq/L	94 mEq/L
Bicarbonate	26 mEq/L	22 mEq/L
Blood urea nitrogen	16 mg/dL	26 mg/dL
Creatinine	1.1 mg/dL	2.4 mg/dL

Urine sediment microscopy reveals muddy brown casts. Which of the following renal structures are most likely to demonstrate signs of ischemic injury?

- A. Collecting ducts (4%)
- ✗ B. Distal tubules (7%)
- C. Glomeruli (6%)
- ✓ D. Proximal tubules (72%)
- E. Renal papillae (9%)

Incorrect
Correct answer
D

72%
Answered correctly

07 secs
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Explanation

This patient most likely has **acute tubular necrosis** (ATN) due to decreased renal perfusion during cardiac arrest (cardiogenic shock). Ischemic kidney injury predominantly affects the **renal medulla**, which has low blood supply even under normal conditions. The most metabolically active segments of the nephron are particularly vulnerable, including the **proximal tubule** and **thick ascending limb** of the loop of Henle.

ATN is characterized histologically by flattening of the tubular epithelial cells with loss of the brush border and subsequent cell necrosis and denudation of the tubular basement membrane. Muddy brown casts consisting of sloughed and degenerated tubule cells are pathognomonic for ATN. Patients frequently have **increased serum creatinine**, a blood urea nitrogen/serum creatinine ratio <20 (indicating intrinsic renal pathology), and **oliguria**.

(Choices A and B) The distal tubules are located in the renal cortex, and the collecting ducts are in the cortex and medulla. They are less likely to show signs of ischemic injury because they are less metabolically active than the proximal tubules or the thick ascending limb of the loop of Henle.

(Choice C) The increased distal sodium delivery caused by tubular dysfunction in ATN leads to afferent arteriolar constriction via the tubuloglomerular feedback mechanism. This can further reduce medullary blood flow and worsen tubular ischemic damage. However, the glomeruli themselves are less susceptible to ischemic injury because of their low metabolic activity.

(Choice E) Renal papillary blood supply may be interrupted by urinary tract obstruction/infection, interstitial nephritis due to analgesic ingestion, or microvascular disease (eg, diabetes mellitus, sickle cell disease). However, renal papillary necrosis typically presents with gross hematuria and flank pain.

Educational objective:
Acute tubular necrosis can be caused by renal ischemia and is characterized by oliguria, increased serum creatinine, and muddy brown casts. Ischemic injury predominantly affects the renal medulla, which has a relatively low blood supply. The proximal tubules and the thick ascending limb of the loop of Henle are the most commonly

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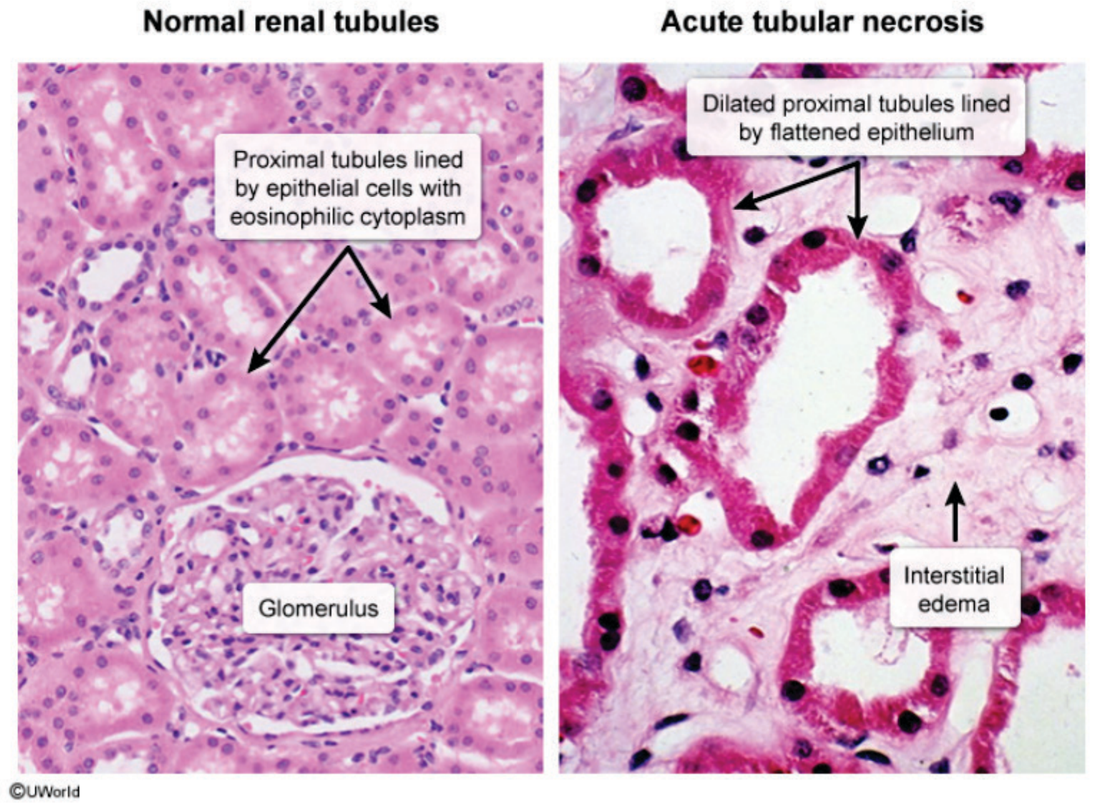
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Acute tubular necrosis can be caused by renal ischemia and is characterized by oliguria, increased serum creatinine, and muddy brown casts. Ischemic injury predominantly affects the renal medulla, which has a relatively low blood supply. The proximal tubules and the thick ascending limb of the loop of Henle are the most commonly involved portions of the nephron.

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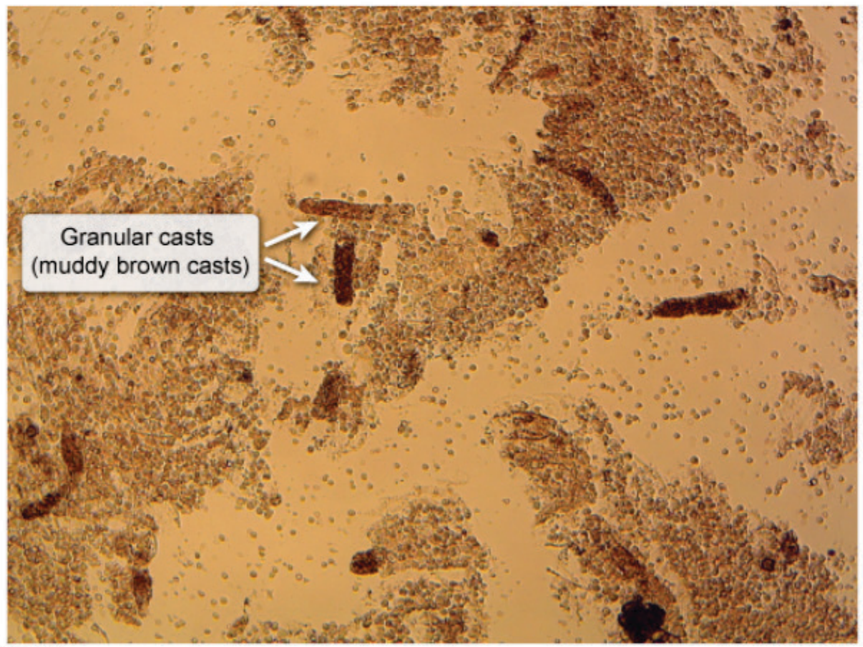
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Acute tubular necrosis



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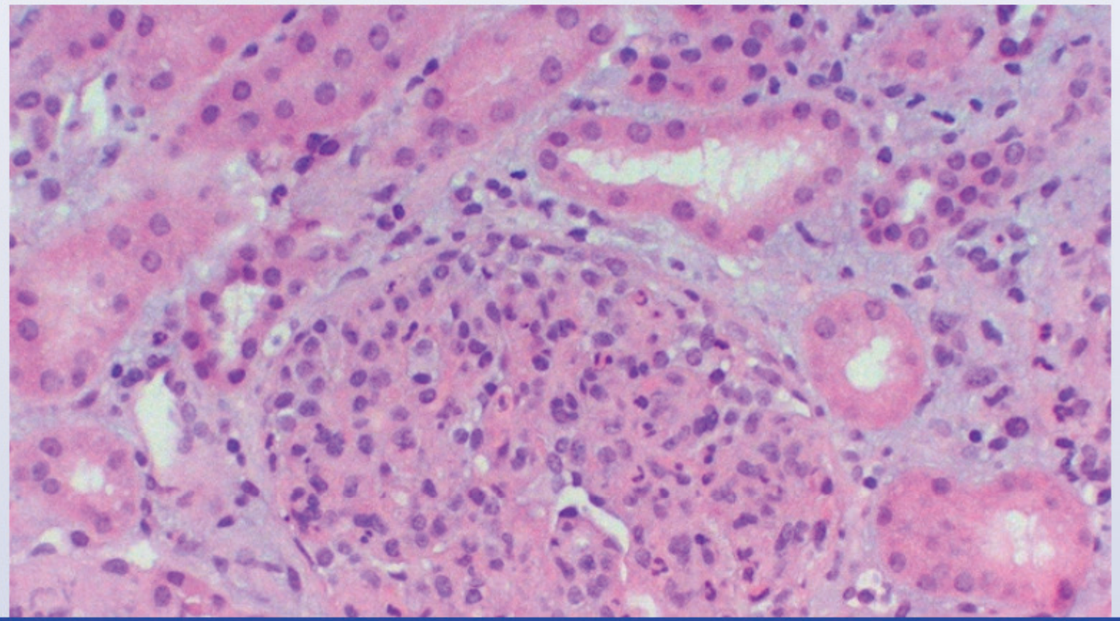
renal papillary necrosis typically presents with gross hematuria and flank pain.

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A 12-year-old boy is brought to the clinic because of facial puffiness. Examination shows periorbital edema. Urinalysis reveals:

Protein	1+
Blood	trace
White blood cells	3-5/hpf
Red blood cells	20-30/hpf
Casts	red blood cells
Crystals	none

A biopsy image representative of this patient's disease process is shown below.

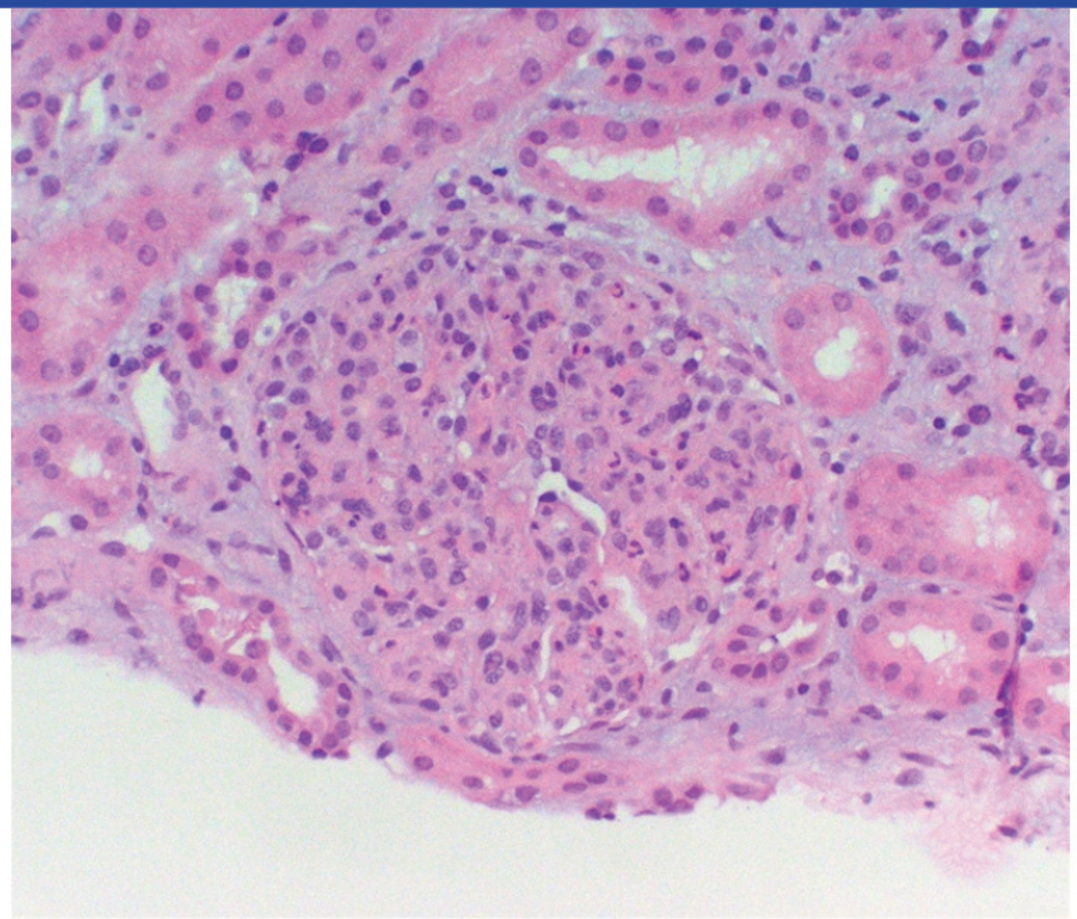


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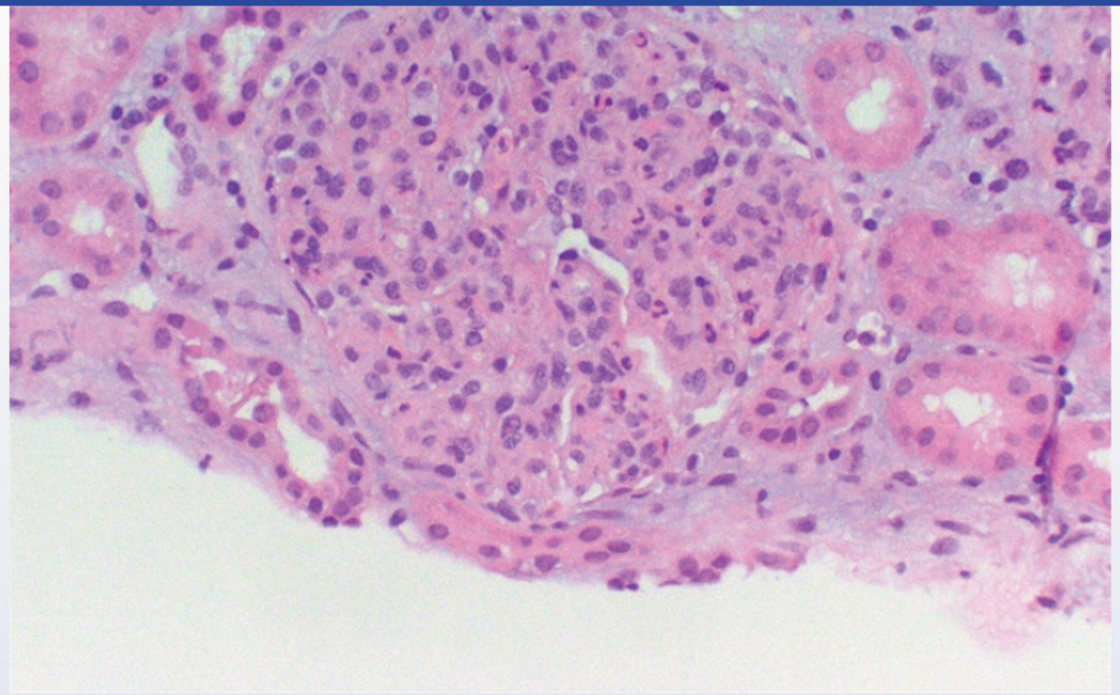
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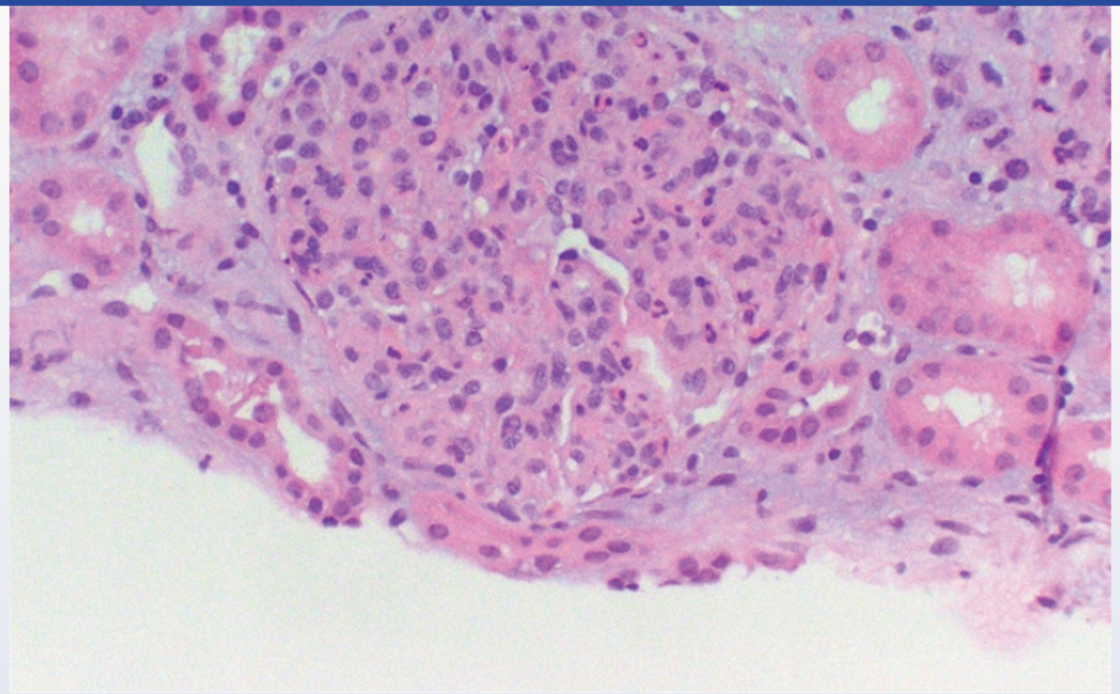


Which of the following additional findings is most likely to be present in this patient?

- A. Antiglomerular basement membrane antibodies
- B. Antineutrophil cytoplasmic antibodies
- C. Decreased serum C3 level
- D. Decreased serum C4 level
- E. Increased eosinophil count

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Which of the following additional findings is most likely to be present in this patient?

- A. Antiglomerular basement membrane antibodies (8%)
- ✗ B. Antineutrophil cytoplasmic antibodies (4%)
- ✓ C. Decreased serum C3 level (77%)
- D. Decreased serum C4 level (3%)
- E. Increased eosinophil count (5%)

Incorrect
Correct answer
C

77%
Answered correctly

15 secs
Time Spent

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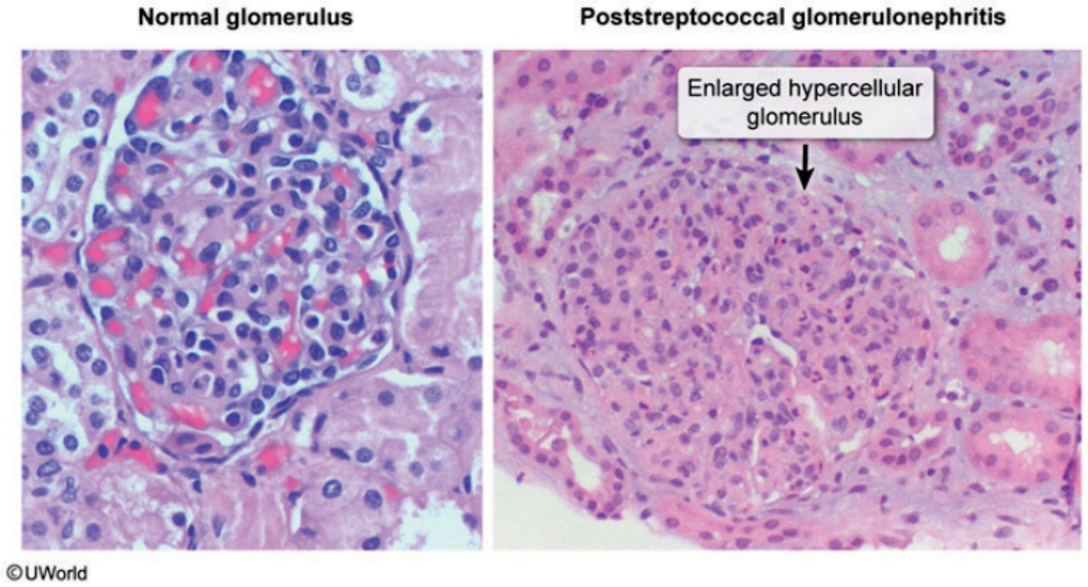
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This pediatric patient with microscopic hematuria, red blood cell casts, mild pyuria, and proteinuria has a nephritic syndrome (glomerulonephritis). The biopsy sample demonstrates **enlarged, hypercellular glomeruli** consistent with **poststreptococcal glomerulonephritis** (PSGN), which is the most common cause of **nephritic syndrome** in children. PSGN is caused by immune complex deposition in the glomerulus following group A beta-hemolytic *Streptococcus* (eg, *Streptococcus pyogenes*) infection. Hypercellularity, which involves all lobules of all glomeruli, is the result of leukocyte infiltration and endothelial and mesangial cell proliferation in response to secreted cytokines.

Other classic findings include elevated titers of antistreptococcal antibodies (eg, antistreptolysin O, anti–DNase B) and **low C3 concentrations** (due to consumption). Electron microscopy typically shows electron-dense deposits composed of immune complexes on the epithelial side of the glomerular basement membrane. On immunofluorescent microscopy, there are coarse, granular deposits of IgG and C3 with a characteristic "starry sky" appearance.

(Choices A and B) Serum antiglomerular basement membrane antibodies are found in Goodpasture syndrome. Serum antineutrophil cytoplasmic antibodies are associated with certain vasculitides (eg, granulomatosis with polyangiitis, microscopic polyangiitis). These conditions can cause both pulmonary-renal syndrome with hemoptysis and renal failure. However, the typical renal manifestation is rapidly progressive glomerulonephritis, which is characterized by crescent formation on light microscopy. In addition, these conditions are rare in children.

(Choice D) Although C3 levels are decreased in almost all patients with PSGN, C4 levels are usually normal as complement activation in PSGN occurs predominantly via the alternative pathway.

(Choice E) Eosinophilia can occur in acute interstitial nephritis, which causes renal failure but is typically associated with fever, rash, sterile pyuria, and white blood cell casts; significant hematuria and red blood cell casts are unexpected.

Educational objective:

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Educational objective:
Poststreptococcal glomerulonephritis is the most common cause of nephritic syndrome in children. Light microscopy demonstrates enlarged, hypercellular glomeruli. Laboratory findings in poststreptococcal glomerulonephritis include elevated antistreptococcal antibodies (eg, antistreptolysin O, anti–DNase B) and decreased C3 and total complement levels. C4 levels are usually normal.

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Nephritic vs nephrotic syndrome		
	Nephritic	**Nephrotic**
Proteinuria	Mild	Significant (>3.5 g/day)
Serum albumin	Normal	Decreased
Edema	Mild	Significant
GFR	Decreased	Normal
Hypertension	Yes	No
Hematuria	Yes	No
Pyuria	Yes	No
Casts	RBC	Fatty or none
GFR = glomerular filtration rate; **RBC** = red blood cell.		

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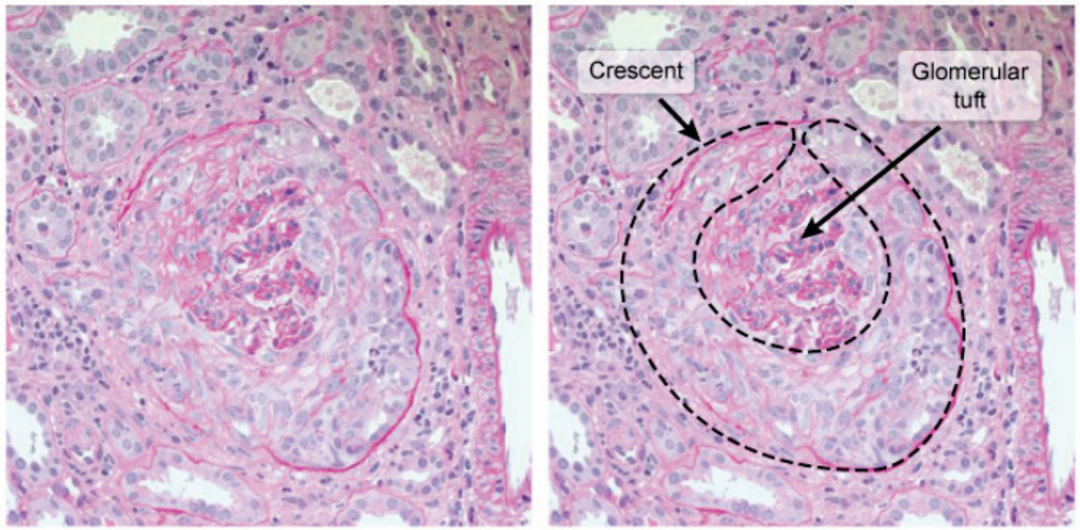
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Poststreptococcal glomerulonephritis is the most common cause of nephritic syndrome in children. Light microscopy demonstrates enlarged, hypercellular glomeruli. Laboratory findings in poststreptococcal

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Crescentic glomerulonephritis



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A 46-year-old previously healthy woman comes to the emergency department due to 4 days of intermittent fever, abdominal pain, and vomiting. For the past 2 days, she has also had decreased urine output, skin rash, and progressive lethargy. Temperature is 38.3 C (101 F), blood pressure is 130/80 mm Hg, and pulse is 100/min. There is a scattered petechial rash, facial puffiness, and 1+ bilateral pedal edema on physical examination. Laboratory results show hemoglobin of 8.9 g/dL with elevated reticulocyte count and a platelet count of 26,000/mm^3. Bleeding time is prolonged; PT and activated PTT are normal. The peripheral blood smear shows schistocytes and reduced platelets with presence of giant forms. Blood urea nitrogen is 46 mg/dL and serum creatinine is 2.3 mg/dL. Urinalysis is positive for proteinuria and hematuria. Which of the following is most likely to be seen on this patient's renal biopsy?

- A. Collapse and sclerosis of glomerular tufts
- B. Crescent-shaped mass of cellular proliferation and leukocytes
- C. Diffuse cellular proliferation and subepithelial immunoglobulin deposits
- D. Mesangial IgA deposition and cellular proliferation
- E. Patchy necrosis of tubular epithelium and loss of basement membrane
- F. Platelet-rich thrombi in glomeruli and arterioles

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- A. Collapse and sclerosis of glomerular tufts (1%)
- ✗ B. Crescent-shaped mass of cellular proliferation and leukocytes (18%)
- C. Diffuse cellular proliferation and subepithelial immunoglobulin deposits (11%)
- D. Mesangial IgA deposition and cellular proliferation (12%)
- E. Patchy necrosis of tubular epithelium and loss of basement membrane (8%)
- ✓ F. Platelet-rich thrombi in glomeruli and arterioles (46%)

Incorrect
Correct answer
F

46%
Answered correctly

31 secs
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Explanation

This patient with a **pentad** of fever, neurologic symptoms (eg, progressive lethargy), renal failure, anemia, and

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Explanation

This patient with a **pentad** of fever, neurologic symptoms (eg, progressive lethargy), renal failure, anemia, and thrombocytopenia has schistocytes on peripheral blood smear, which is indicative of **thrombotic microangiopathy** (TMA) (eg, thrombocytopenic thrombotic purpura [TTP]). TMA syndromes have varying etiologies but share common clinical and pathologic features, including:

- **Platelet activation** in arterioles and capillaries
- Diffuse **microvascular thrombosis** (eg, brain, kidneys, skin, gastrointestinal tract)
- Organ ischemia and dysfunction (eg, headache, hematuria, petechial rash, abdominal pain)
- Microangiopathic hemolytic anemia with **schistocytes** (red blood cells fragmented by microthrombi)
- **Thrombocytopenia** due to platelet consumption

Unlike disseminated intravascular coagulation, in which coagulation cascade activation leads to prolongation of coagulation studies (PT and activated PTT), TTP is almost always characterized by **normal PT and activated PTT**. The diagnosis can be confirmed with histopathology, which typically shows thrombi in small blood vessels (eg, glomerular capillaries, arterioles).

(Choice A) Histopathology in focal segmental glomerulosclerosis shows collapse and sclerosis of a segment of the glomerular tuft and characteristically affects some, but not all, glomeruli. Although it commonly manifests with proteinuria and edema, thrombocytopenia and anemia with schistocytes would not be expected.

(Choice B) Crescent formation is characteristic of rapidly progressive glomerulonephritis, which typically presents with macroscopic hematuria, hypertension, and progressive renal failure; it is caused by severe immunologic injury (eg, anti–glomerular basement membrane antibodies, immune complex deposition). This patient's thrombocytopenia and anemia with schistocytes are more suggestive of TMA.

(Choice C) Poststreptococcal glomerulonephritis is microscopically characterized by hypercellular glomeruli with

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(Choice C) Poststreptococcal glomerulonephritis is microscopically characterized by hypercellular glomeruli with subepithelial immune deposits. It typically affects children following streptococcal infection and can lead to increased cola-colored urine output and periorbital edema.

(Choice D) Henoch-Schönlein purpura is typically a childhood disease with nonthrombocytopenic palpable purpura and arthralgias; IgA nephropathy commonly presents with recurrent hematuria and low-grade proteinuria following an upper respiratory tract infection. Both diseases show IgA deposition in the mesangium.

(Choice E) Acute tubular necrosis due to ischemia (eg, prolonged hypotension) or nephrotoxins (eg, antibiotics, myoglobin) generally presents with rising creatinine and muddy brown granular casts on urinalysis.

Educational objective:
Primary thrombotic microangiopathy (TMA) syndromes share common clinical and pathologic features and result in platelet activation and diffuse microthrombosis in arterioles and capillaries. They present with hemolytic anemia, schistocytes, thrombocytopenia, and organ injury (eg, brain, kidneys).

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This patient with a **pentad** of fever, neurologic symptoms (eg, progressive lethargy), renal failure, anemia, and thrombocytopenia has schistocytes on peripheral blood smear, which is indicative of **thrombotic mic** etiol

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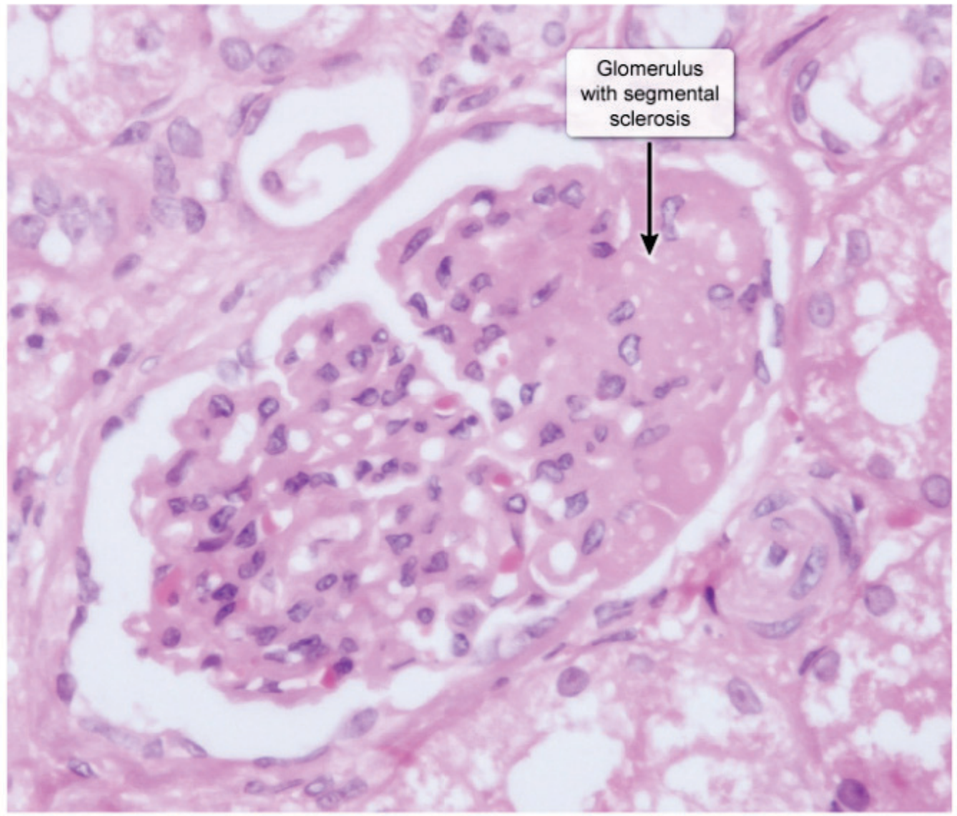
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(Choice D) Henoch-Schönlein purpura is typically a childhood disease with nonthrombocytopenic palpable

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Focal segmental glomerulosclerosis



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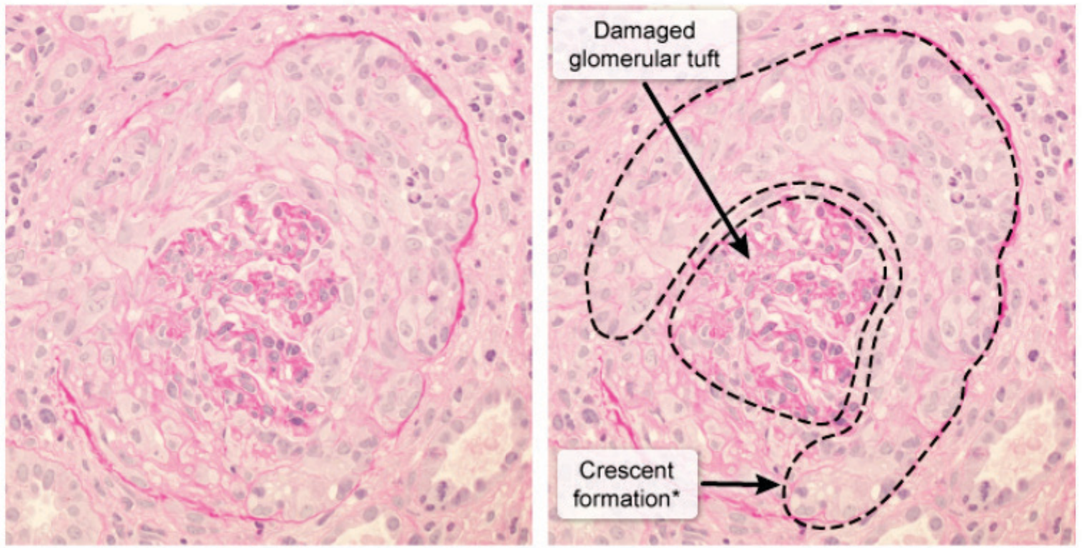
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Rapidly progressive (crescentic) glomerulonephritis



*Crescent formed by glomerular epithelial cells, macrophages, and fibrin.

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- Organ ischemia and dysfunction (eg, headache, hematuria, petechial rash, abdominal pain)
- Microangiopathic hemolytic anemia with **schistocytes** (red blood cells fragmented by microthrombi)
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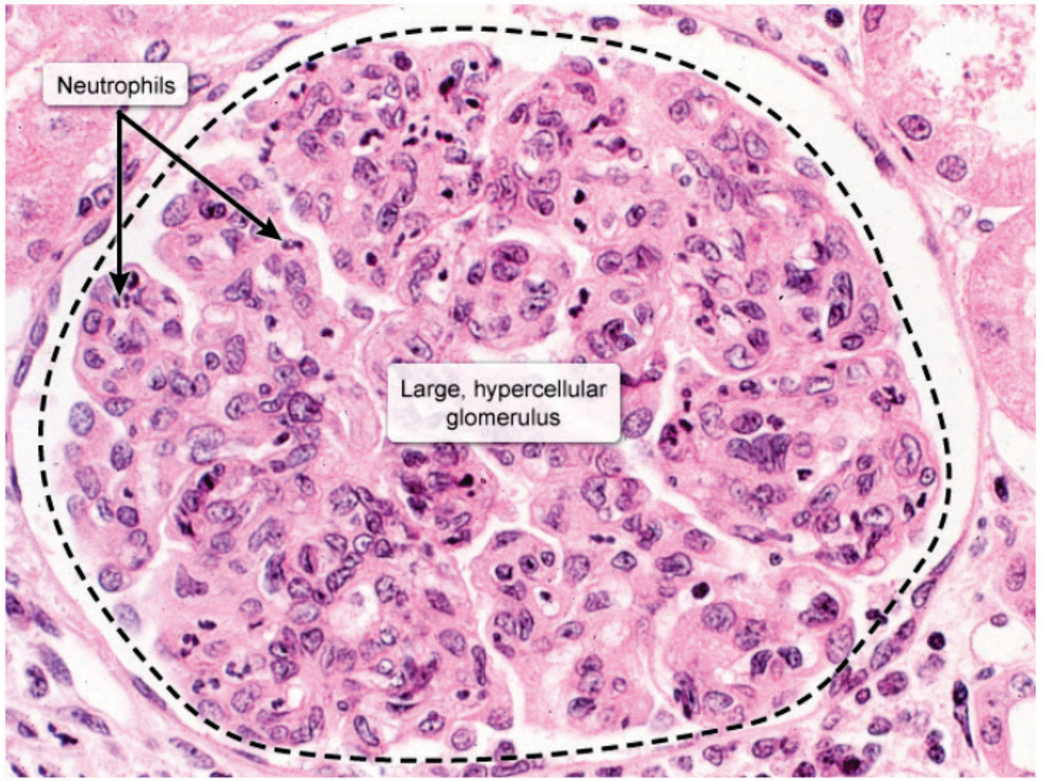
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Educational objective:

Primary thrombotic microangiopathy (TMA) syndromes share common clinical and pathologic features and result in

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Poststreptococcal glomerulonephritis



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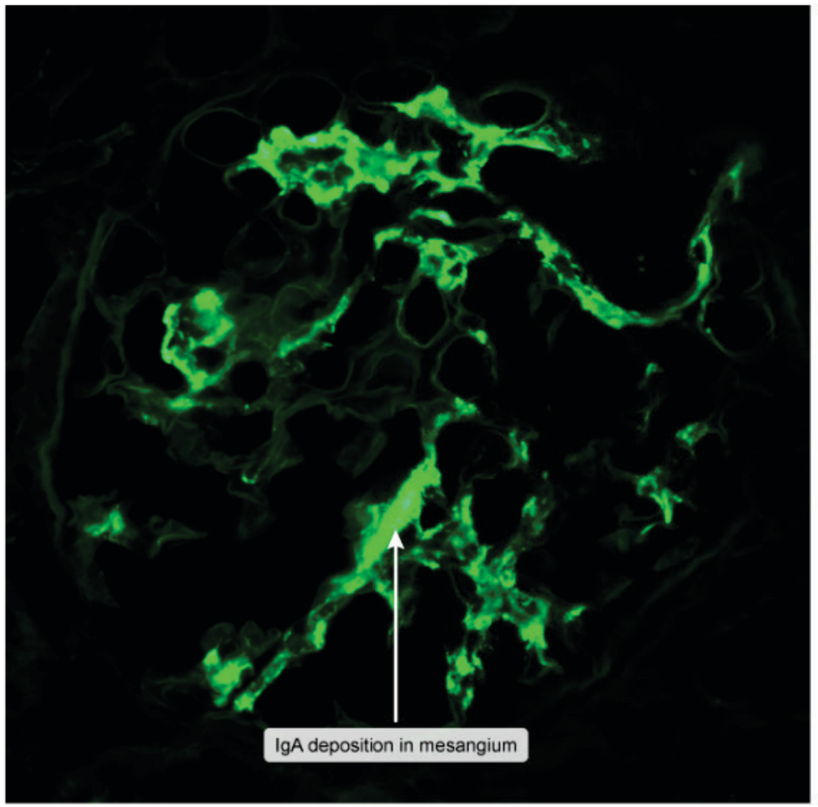
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- Organ ischemia and dysfunction (eg, headache, hematuria, petechial rash, abdominal pain)

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IgA nephropathy



Immunofluorescence

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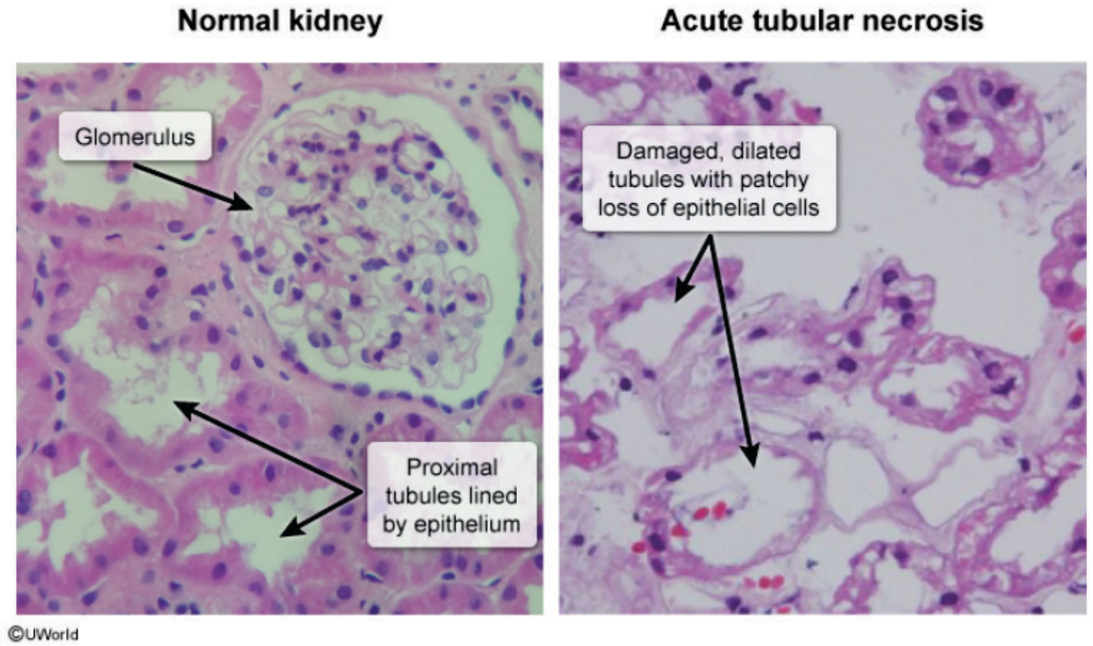
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Educational objective:

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- Organ ischemia and dysfunction (eg, headache, hematuria, petechial rash, abdominal pain)

Exhibit Display



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Educational objective:

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A 7-year-old boy is brought to the emergency department due to bloody stools. The patient first developed colicky abdominal pain 2 days ago, and he had blood in a bowel movement today. His urine also appeared red. He has had no diarrhea, vomiting, or dysuria. The boy has no significant medical history, and his vaccinations are up to date. Temperature is 37.2 C (99 F), pulse is 120/min, and respirations are 20/min. The oropharynx is clear, and the neck is supple. Cardiopulmonary examination is unremarkable. The abdomen is diffusely tender with active bowel sounds. There are raised, purple-red skin lesions along the buttocks and lower extremities. Which of the following additional findings is most likely present in this patient?

- A. Generalized lymphadenopathy
- B. Honey-crusted skin rash
- C. Injected conjunctivae
- D. Joint pain
- E. Painful oral ulcers

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- A. Generalized lymphadenopathy (8%)
- ✗ B. Honey-crusted skin rash (5%)
- C. Injected conjunctivae (7%)
- ✓ D. Joint pain (73%)
- E. Painful oral ulcers (6%)

Incorrect
Correct answer
D

73%
Answered correctly

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Time Spent

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Explanation

IgA vasculitis (Henoch-Schönlein purpura)	
Pathogenesis	• Deposition of IgA immune complexes in small vessels activates complement • Neutrophilic inflammation & vascular damage • Often follows an upper respiratory infection

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IgA vasculitis (Henoch-Schönlein purpura)	
Pathogenesis	• Deposition of IgA immune complexes in small vessels activates complement • Neutrophilic inflammation & vascular damage • Often follows an upper respiratory infection
Clinical manifestations	• Palpable purpura/petechiae on the lower extremities • Arthritis/arthralgia • Abdominal pain, gastrointestinal bleeding, intussusception • Renal disease (hematuria ± proteinuria)
Diagnosis	• Usually clinical • Skin biopsy: leukocytoclastic vasculitis, IgA deposition in vessel walls

This patient has classic signs of **Henoch-Schönlein purpura** (HSP), an IgA-mediated leukocytoclastic vasculitis that is most commonly seen in children.

HSP predominantly affects the small vessels of the following organ systems:

- **Skin:** The most common initial manifestation is **palpable purpura** on the buttocks and lower extremities.
- **Gastrointestinal (GI) tract:** Intermittent **colicky abdominal pain** is typical. Bowel wall edema and hemorrhage can also lead to **GI bleeding** (eg, hematemesis, bloody stools) and serve as a lead point for intussusception.
- **Kidneys:** Patients most commonly have gross or microscopic hematuria. Renal pathology in HSP is characterized by mesangial proliferation and IgA deposition (identical to findings seen in IgA nephropathy).
- **Joints:** Transient or migratory **arthralgia or arthritis** usually occurs in the hips, knees, and ankles.

Therefore, the most likely additional finding in this patient with palpable purpura, abdominal pain, and gross hematuria is joint pain.

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This patient has classic signs of **Henoch-Schönlein purpura** (HSP), an IgA-mediated leukocytoclastic vasculitis that is most commonly seen in children.

HSP predominantly affects the small vessels of the following organ systems:

- **Skin:** The most common initial manifestation is **palpable purpura** on the buttocks and lower extremities.
- **Gastrointestinal (GI) tract:** Intermittent **colicky abdominal pain** is typical. Bowel wall edema and hemorrhage can also lead to **GI bleeding** (eg, hematemesis, bloody stools) and serve as a lead point for intussusception.
- **Kidneys:** Patients most commonly have gross or microscopic hematuria. Renal pathology in HSP is characterized by mesangial proliferation and IgA deposition (identical to findings seen in IgA nephropathy).
- **Joints:** Transient or migratory **arthralgia or arthritis** usually occurs in the hips, knees, and ankles.

Therefore, the most likely additional finding in this patient with palpable purpura, abdominal pain, and gross hematuria is joint pain.

(Choice A) Generalized lymphadenopathy is suggestive of certain acute, viral infections such as Epstein-Barr virus (EBV) or hematologic malignancy (eg, leukemia). EBV can cause abdominal pain and a maculopapular or petechial rash in association with fever; bloody stools, hematuria, or palpable purpura are not characteristic. Hematologic malignancy can result in easy bruising and bleeding, but presentation usually includes hepatosplenomegaly and/or systemic symptoms (eg, fever, weight loss). In contrast, HSP is not associated with generalized lymphadenopathy, although localized cervical lymphadenopathy may be present due to a preceding upper respiratory infection in some patients.

(Choice B) Poststreptococcal glomerulonephritis (PSGN) presents with gross hematuria weeks after (not in conjunction with) a streptococcal infection such as impetigo, a honey-colored crusted skin rash. Moreover, PSGN is not associated with bloody stools or purpura.

(Choice C) Conjunctival injection is a classic feature of adenovirus infection and is typically associated with fever

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(Choice C) Conjunctival injection is a classic feature of adenovirus infection and is typically associated with fever and pharyngitis, neither of which is seen here. Moreover, although certain serotypes of adenovirus can cause hematuria due to hemorrhagic cystitis or abdominal pain due to gastroenteritis, palpable purpura is not associated with any adenovirus infection.

(Choice E) Aphthous ulcers can occur with Crohn disease, which often presents with abdominal pain and bloody stools. However, hematuria and purpura would not be expected.

Educational objective:
Henoch-Schönlein purpura is an IgA-mediated leukocytoclastic vasculitis that commonly causes lower extremity palpable purpura, abdominal pain (± gastrointestinal bleeding), renal disease (eg, hematuria), and joint pain.

References

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A 65-year-old man comes to the office with a 2-day history of skin rash and low-grade fever. He has had no cough, shortness of breath, chest pain, vomiting, dysuria, or urinary frequency. The patient was recently diagnosed with acute gouty arthritis and has been taking indomethacin for the past 10 days. Temperature is 38.1 C (100.6 F), blood pressure is 130/90 mm Hg, and pulse is 86/min. Examination shows a diffuse, maculopapular skin rash. Mucosal surfaces are moist without any lesions. Cardiopulmonary examination shows no abnormities. There is no costovertebral angle tenderness. Serum creatinine is 2.3 mg/dL (baseline 1.1 mg/dL, 2 weeks ago). Urinalysis shows numerous white blood cells/hpf. Which of the following is the most likely cause of this patient's acute renal dysfunction?

- A. Interstitial nephritis
- B. Pyelonephritis
- C. Renal tubular necrosis
- D. Stevens-Johnson syndrome
- E. Uric acid nephropathy

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- ✓ A. Interstitial nephritis (78%)
- ✗ B. Pyelonephritis (4%)
- C. Renal tubular necrosis (6%)
- D. Stevens-Johnson syndrome (6%)
- E. Uric acid nephropathy (3%)

Incorrect
Correct answer
A

78%
Answered correctly

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Explanation

Acute interstitial nephritis	
	• **Antibiotics** (eg, beta-lactam, sulfonamide, rifampin) • Proton pump inhibitors

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Acute interstitial nephritis	
Causes	• **Antibiotics** (eg, beta-lactam, sulfonamide, rifampin) • Proton pump inhibitors • NSAIDs • Diuretics • Other: Autoimmune diseases, *Mycoplasma*, *Legionella*
Clinical features	• Rash, fever, or asymptomatic • New drug exposure
Laboratory findings	• Acute kidney injury • Pyuria, hematuria, WBC casts • Eosinophilia, **urinary eosinophils** • Renal biopsy: Inflammatory interstitial infiltrate and edema
NSAIDs = nonsteroidal anti-inflammatory drugs; **WBC** = white blood cell.	

This patient has a rash, fever, acute kidney injury, and pyuria following the introduction of indomethacin, which is consistent with **acute interstitial nephritis** (AIN). AIN is a common cause of renal dysfunction and is characterized by an inflammatory infiltration of the renal interstitium, likely due to IgE- and T-cell–mediated hypersensitivity reactions.

Up to 75% of AIN cases are due to medications, particularly **nonsteroidal anti-inflammatory drugs** (eg, indomethacin), antibiotics (eg, penicillins, rifampin), diuretics, and proton pump inhibitors. Clinical features of AIN resemble an allergic response and include **fever**, **rash**, and eosinophilia. Urinalysis typically demonstrates sterile **pyuria**; white blood cell casts, hematuria, and mild proteinuria may also be seen. The presence of urine eosinophils is a supportive but nonspecific finding as eosinophiluria can occur in other diseases (eg, transplant

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(Choice B) Pyelonephritis can cause pyuria and fever, but patients typically have dysuria, flank pain, costovertebral tenderness, and symptoms of systemic toxicity (eg, nausea, vomiting, hypotension). In addition, rash would be unexpected.

(Choice C) Acute tubular necrosis is often caused by ischemic (eg, hypotension) or toxic (eg, radiocontrast) injury to the renal tubular cells. Urinalysis typically demonstrates muddy brown, granular casts, not pyuria.

(Choice D) Stevens-Johnson syndrome can cause fever and rash after initiation of a new medication; however, the rash is typically painful, macular, and progressive, with bullae formation and sloughing of the skin. Mucosal surfaces (ie, oral, ocular) are typically involved.

(Choice E) Acute uric acid nephropathy (due to crystallization of uric acid within the renal tubules) typically occurs in patients with tumor lysis syndrome, which often occurs in leukemia and lymphomas (particularly during chemotherapy). Uric acid crystals are typically seen on urinalysis, and rash would be unexpected.

Educational objective:
Acute interstitial nephritis is a common cause of renal dysfunction; up to 75% of cases are due to medications including nonsteroidal anti-inflammatory drugs, antibiotics, diuretics, and proton pump inhibitors. Presenting

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hypersensitivity reactions.

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Educational objective:
Acute interstitial nephritis is a common cause of renal dysfunction; up to 75% of cases are due to medications including nonsteroidal anti-inflammatory drugs, antibiotics, diuretics, and proton pump inhibitors. Presenting features include fever, rash, and eosinophilia. Urinalysis often demonstrates pyuria and white blood cell casts with elevated urine eosinophils.

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A 34-year-old woman comes to the hospital with a 4-day history of abdominal cramps, nausea, and watery diarrhea. Today she developed dizziness on standing. Her child has had similar symptoms recently. The patient has no prior medical conditions and takes no medications on a regular basis. Blood pressure is 124/82 mm Hg while supine and 100/70 on standing; pulse is 98/min. Examination shows dry mucous membranes. The abdomen is soft and nontender. Laboratory results are as follows:

Serum chemistry	
Sodium	144 mEq/L
Blood urea nitrogen	50 mg/dL
Creatinine	1.8 mg/dL
Urinalysis	
Protein	negative
Red blood cells	0/hpf
White blood cells	0-1/hpf
Microscopy	few hyaline casts
Urine sodium	8 mEq/L

Which of the following changes are most likely to be seen in this patient?

	Vasopressin	Norepinephrine	Angiotensin II	Endothelin 1
○ A.	↑	↑	↑	↑

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Blood urea nitrogen	50 mg/dL
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	Vasopressin	Norepinephrine	Angiotensin II	Endothelin 1
A.	↑	↑	↑	↑
B.	↑	↑	↑	↓
C.	↓	↑	↑	↓
D.	↑	↓	↓	↑
E.	↓	↓	↓	↓
F.	↑	↓	↑	↓

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Protein	negative
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Microscopy	few hyaline casts
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Which of the following changes are most likely to be seen in this patient?

	Vasopressin	Norepinephrine	Angiotensin II	Endothelin 1	
✓ A.	↑	↑	↑	↑	(51%)
✗ B.	↑	↑	↑	↓	(27%)
C.	↓	↑	↑	↓	(6%)
D.	↑	↓	↓	↑	(5%)
E.	↓	↓	↓	↓	(4%)
F.	↑	↓	↑	↓	(5%)

Incorrect
Correct answer
A

51%
Answered correctly

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This patient with gastroenteritis has evidence of **hypovolemia** (dry mucous membranes, orthostatic dizziness/hypotension) and acute kidney injury. Decreased extracellular fluid volume stimulates compensatory mechanisms directed at maintaining systemic blood pressure and tissue oxygenation. This is largely driven by the sympathetic nervous system and the kidneys:

- Activation of the **renin-angiotensin-aldosterone system** (RAAS) leads to elevated levels of **angiotensin II** (ATII), a potent vasoconstrictor that stimulates the release of aldosterone and **endothelin 1**. These increase sodium and water reabsorption and systemic vascular resistance to help maintain blood pressure.
- **Vasopressin** (antidiuretic hormone) is released by the posterior pituitary in response to increased serum osmolarity and decreased systemic pressure; it increases urea and free water reabsorption by the renal collecting duct.
- **Increased sympathetic activity** results in release of circulating **norepinephrine** and other catecholamines, which increases systemic vasoconstriction, renal sodium and water reabsorption, and heart rate.

These neurohumoral mechanisms promote volume expansion and increase blood pressure, helping to maintain tissue perfusion. Laboratory studies characteristically reflect sodium, water, and urea reabsorption by the kidney, including **low urine sodium** (<20 mEq/L), low fractional excretion of sodium (<1%), and **elevated blood urea nitrogen to creatinine ratio** (>20:1). Urinary sediment is typically bland or may show hyaline casts (which suggest increased urine concentration).

Educational objective:
Hypovolemia triggers a variety of compensatory mechanisms to improve tissue perfusion. These include activation of the renin-angiotensin-aldosterone system (resulting in increased aldosterone and endothelin release), increased vasopressin release, and increased sympathetic tone.

Pathophysiology	Renal, Urinary Systems & Electrolytes	Prerenal azotemia

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A 46-year-old man comes to the emergency department with flank pain and hematuria. The pain is similar to several previous episodes of kidney stones. Abdominal imaging reveals a radiopaque calculus in the right ureter. The patient is admitted to the hospital and given intravenous hydration and analgesics. He subsequently passes the stone with rapid relief of his symptoms. Chemical analysis reveals that the stone is composed primarily of calcium oxalate. Which of the following medications is most likely to prevent recurrent stone formation in this patient?

- A. Acetazolamide
- B. Furosemide
- C. Hydrochlorothiazide
- D. Mannitol
- E. Triamterene

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- A. Acetazolamide (10%)
- ✕ B. Furosemide (10%)
- ✓ C. Hydrochlorothiazide (73%)
- D. Mannitol (1%)
- E. Triamterene (2%)

Incorrect
Correct answer
C

73%
Answered correctly

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Time Spent

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Explanation

Effect of thiazide diuretics on distal tubular calcium reabsorption

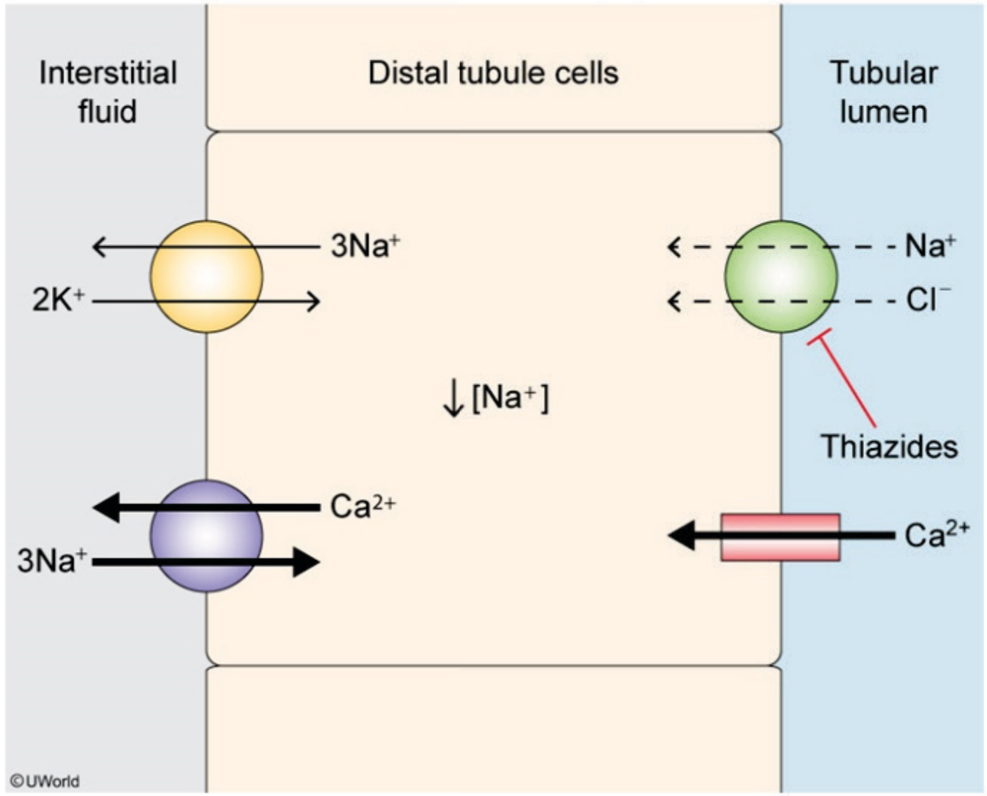
Interstitial fluid	Distal tubule cells	Tubular lumen

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B. Furosemide (10%)

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Effect of thiazide diuretics on distal tubular calcium reabsorption



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Hypercalciuria increases the formation of calcium (calcium oxalate and calcium phosphate) stones, the most common types of kidney stone. In patients with recurrent calcium nephrolithiasis, **thiazide diuretics** can help prevent stone formation by decreasing urine Ca^{2+} excretion.

Thiazides increase Ca^{2+} reabsorption through 2 major mechanisms:

1. **Inhibition of the Na^+/Cl^- cotransporter** on the apical side of distal convoluted tubule cells decreases intracellular Na^+ concentrations. This activates the basolateral Na^+/Ca^{2+} antiporter, which pumps Na^+ into the cell in exchange for Ca^{2+}. The resulting decrease in intracellular Ca^{2+} concentration enhances luminal Ca^{2+} reabsorption across the apical membrane.
2. **Hypovolemia** induced by thiazides increases Na^+ and H_2O reabsorption in the proximal tubule, leading to a passive increase in paracellular Ca^{2+} reabsorption.

(Choice A) Acetazolamide is a carbonic anhydrase inhibitor that acts on the proximal convoluted tubule to cause bicarbonate wasting, raising urine pH and decreasing the risk of uric acid stones. However, the resulting systemic acidosis may increase release of calcium phosphate from bone, which is then cleared by the kidneys. Some studies have found that acetazolamide use may raise the risk of calcium stone formation.

(Choice B) Ca^{2+} reabsorption in the loop of Henle occurs through both the transcellular and paracellular pathways. Paracellular Ca^{2+} reabsorption depends on concurrent, transcellular $Na^+/K^+/Cl^-$ reabsorption. Loop diuretics (eg, furosemide) block the Na-K-2Cl cotransporter and increase urinary Ca^{2+} excretion.

(Choice D) Mannitol is an osmotic diuretic. It is not used as maintenance therapy for any indication as it causes volume depletion and hypernatremia with prolonged use. It has no effect on Ca^{2+} homeostasis.

(Choice E) Triamterene and amiloride are potassium-sparing diuretics that inhibit Na^+ reabsorption in the collecting duct by blocking the epithelial sodium channel. This decreases net Na^+/K^+ exchange, reducing serum K^+ losses.

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Educational objective:
Thiazide diuretics effectively increase renal calcium reabsorption. In patients with recurrent calcium nephrolithiasis, thiazide diuretics can help prevent stone formation by decreasing urine Ca^{2+} excretion.

References

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A 24-year-old woman comes to the office for a routine prenatal ultrasound examination. She is 19 weeks pregnant based on her last menstrual period. This is the patient's third pregnancy, and there have been no complications. Family medical history is unremarkable, and both of the patient's children are healthy. The examination reveals a male fetus with bilaterally enlarged kidneys with diffuse small cysts. The amniotic fluid volume is very low. No other anomalies are seen. Which of the following will most likely be present in the newborn at delivery?

- A. Bladder outlet obstruction
- B. Cerebral aneurysms
- C. Facial hemangiomas
- D. Intestinal atresia
- E. Pulmonary hypoplasia

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- A. Bladder outlet obstruction (9%)
- ✗ B. Cerebral aneurysms (7%)
- C. Facial hemangiomas (1%)
- D. Intestinal atresia (1%)
- ✓ E. Pulmonary hypoplasia (79%)

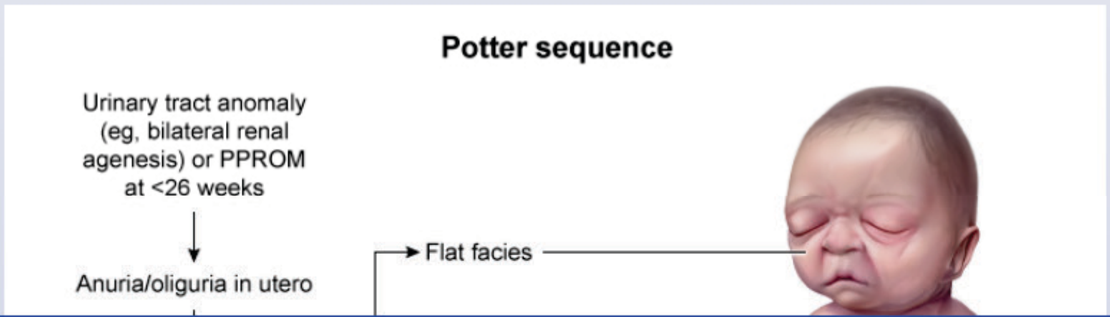
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Correct answer
E

79%
Answered correctly

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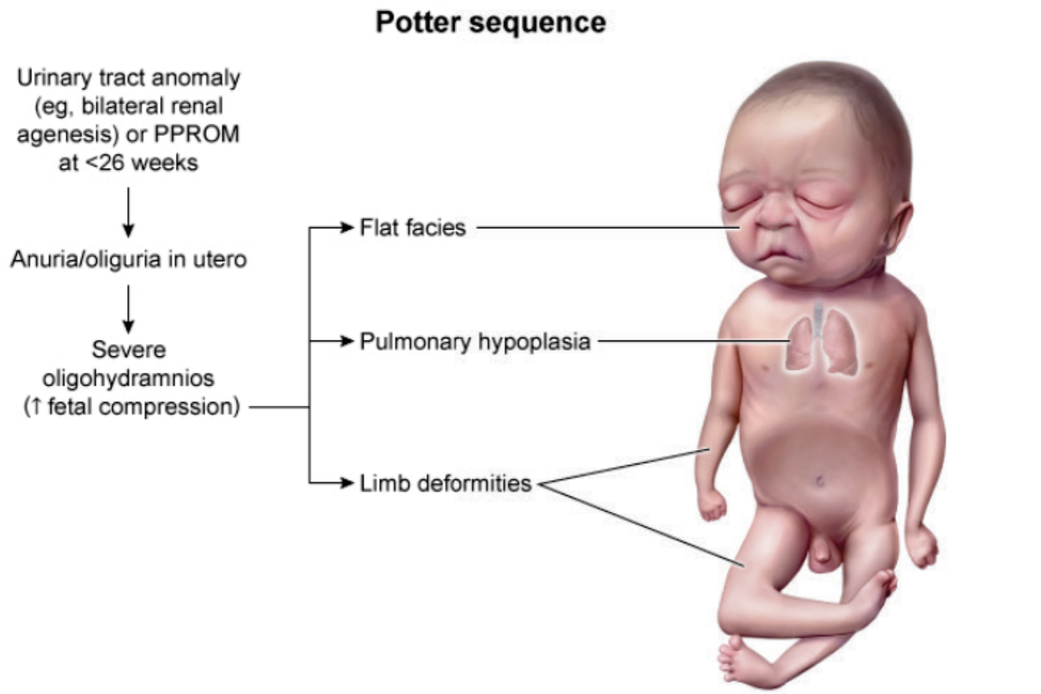
Explanation



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A 24-year-old woman comes to the office for a routine prenatal ultrasound examination. She is 19 weeks pregnant.
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Anuria/oliguria in utero

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This mother has oligohydramnios, and the fetus has bilaterally enlarged cystic kidneys. Because amniotic fluid is largely composed of fetal urine, these findings are concerning for fetal kidney dysfunction and reduced urine production. In this case, the fetus likely has **autosomal recessive polycystic kidney disease** (ARPKD), a condition caused by a mutation in fibrocystin (protein found in epithelial cells of renal tubules). Fibrocystin deficiency leads to diffuse microcysts, as seen here, and impaired kidney function.

Any condition that causes **anuria or oliguria in utero** (eg, ARPKD, bilateral renal agenesis) results in **severe oligohydramnios** and risk of Potter sequence. **Potter sequence** is a predictable series of anomalies caused by fetal compression from insufficient amniotic fluid. Findings include the following:

- **Flattened facies:** Extrinsic fetal compression leads to a flattened, depressed nasal bridge; prominent epicanthal folds; low-set ears; and a recessed chin.
- **Limb deformities:** Restricted fetal movement causes deformities such as contractures, hip dislocation, and clubfoot.
- **Pulmonary hypoplasia:** Restricted thoracic expansion limits fetal lung development, causing respiratory distress and decreased breath sounds after birth. Amniotic fluid is also thought to promote production of elastin, collagen, and vascular endothelial growth factor in fetal lungs, and oligohydramnios likely results in reduced alveolarization and angiogenesis.

Potter sequence is often fatal in infancy, and patients who survive typically develop chronic lung and kidney disease.

(Choice A) Bladder outlet obstruction (eg, posterior urethral valves) causes bladder distension, bilateral hydronephrosis, and in severe cases impaired kidney function and oligohydramnios. However, in contrast to this case, renal cysts would not be present.

(Choice B) Cerebral aneurysms are a common complication of autosomal dominant polycystic kidney disease. However, most patients remain asymptomatic until adulthood; ARPKD is much more likely in this neonate with

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- **Pulmonary hypoplasia:** Restricted thoracic expansion limits fetal lung development, causing respiratory distress and decreased breath sounds after birth. Amniotic fluid is also thought to promote production of elastin, collagen, and vascular endothelial growth factor in fetal lungs, and oligohydramnios likely results in reduced alveolarization and angiogenesis.

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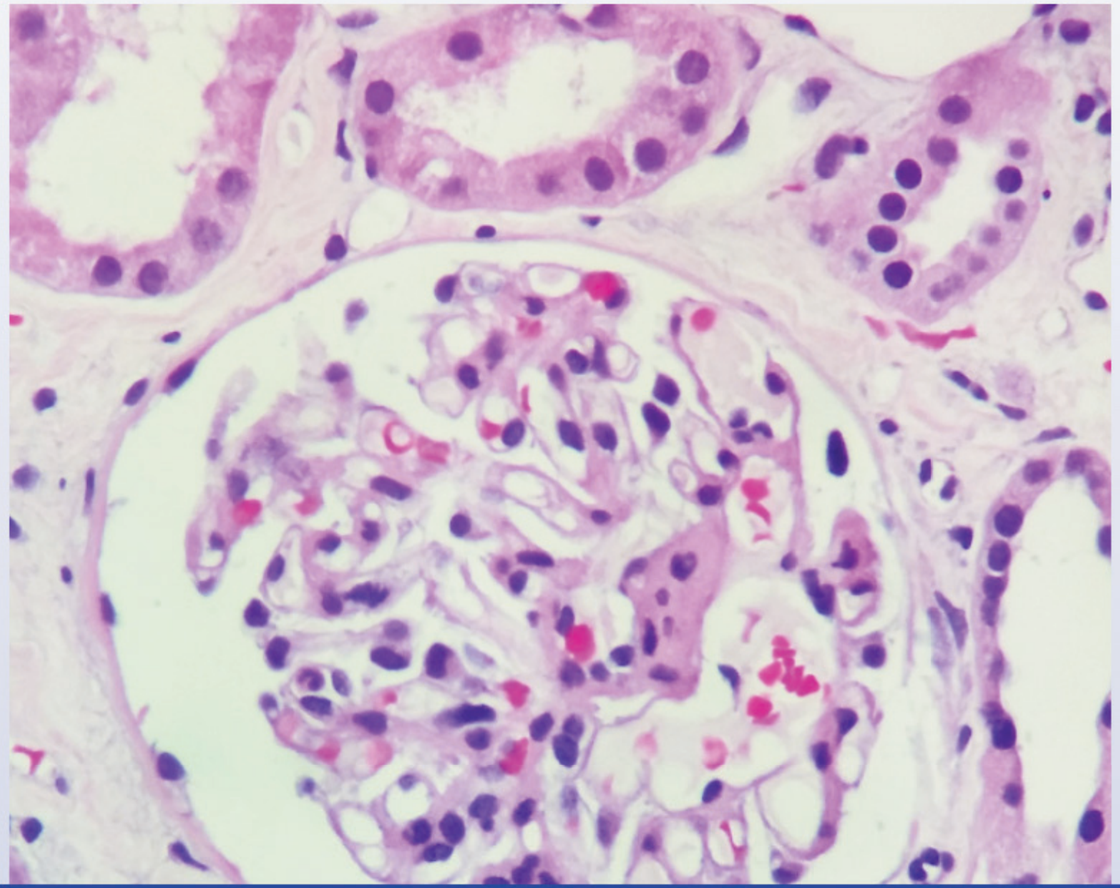
(Choice C) Segmental facial hemangiomas may be associated with other anomalies, as in the PHACE syndrome (abnormalities of the **P**osterior fossa; **H**emangiomas; and **A**rterial cerebrovascular, **C**ardiac, and **E**ye anomalies). Vascular tumors are not associated with ARPKD or Potter sequence.

(Choice D) Intestinal atresia is associated with excessive, not reduced, amniotic fluid (polyhydramnios) due to impaired fluid absorption by the fetal gastrointestinal tract. Furthermore, this patient's renal findings would not be expected in a patient with intestinal atresia.

Educational objective:
Amniotic fluid is largely composed of fetal urine, and oligohydramnios (low fluid) is often associated with kidney dysfunction in the fetus (eg, diffuse cysts seen in autosomal recessive polycystic kidney disease). Extrinsic fetal compression from a low amniotic fluid level leads to Potter sequence with characteristic findings of flattened facies, limb deformities, and pulmonary hypoplasia.

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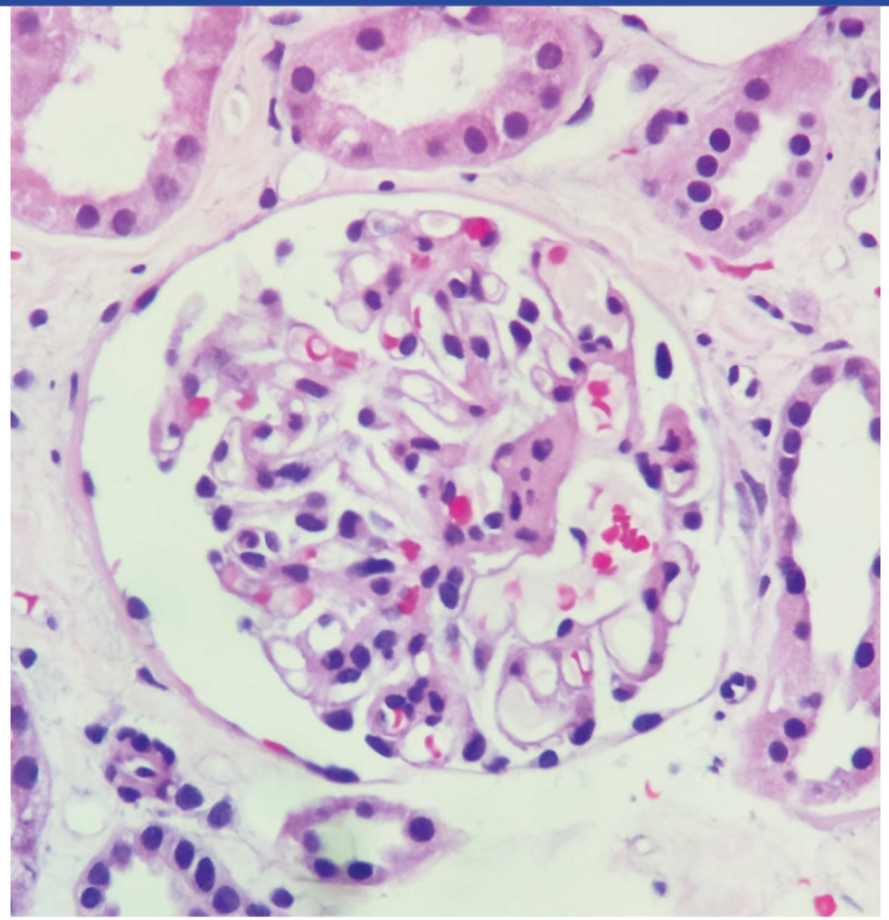
A 15-year-old girl is brought to the clinic for evaluation of swelling around her eyes that developed over the past week. The patient is a cheerleader, and she had been taking ibuprofen daily for the last 3 months for various sprains and aches after practice. She has no chronic medical conditions. Vital signs are normal. On physical examination, there is moderate periorbital edema with bilateral lower extremity pitting edema. Serum creatinine is 0.5 mg/dL and serum albumin is 2.1 g/dL. Urinalysis shows 4+ protein and negative blood. Multiple regions of the kidney are biopsied, and a representative image is shown below:



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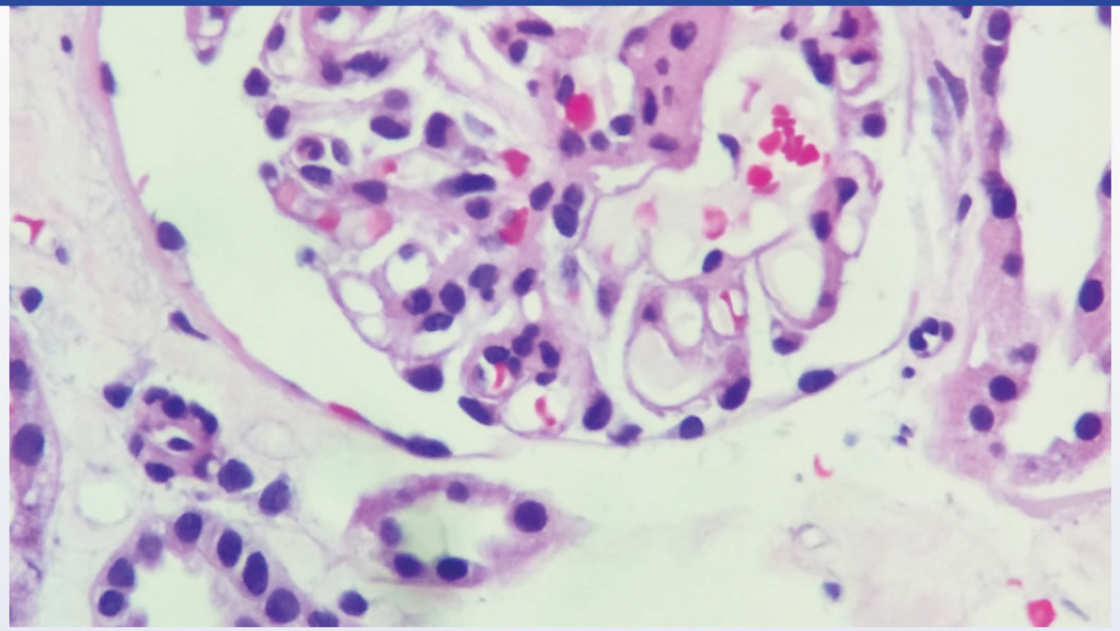
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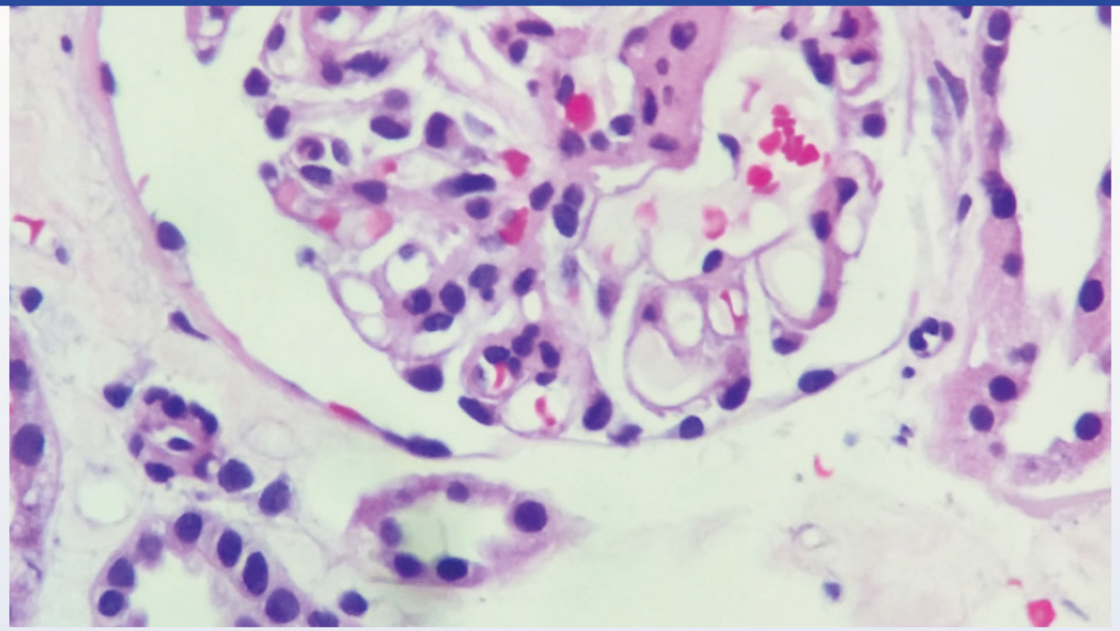


Which of the following is the most likely diagnosis?

- A. Acute interstitial nephritis
- B. Crescentic glomerulonephritis
- C. Focal segmental glomerulosclerosis
- D. Membranous nephropathy
- E. Minimal change disease
- F. Poststreptococcal glomerulonephritis

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Which of the following is the most likely diagnosis?

- A. Acute interstitial nephritis (18%)
- ✗ B. Crescentic glomerulonephritis (2%)
- C. Focal segmental glomerulosclerosis (11%)
- D. Membranous nephropathy (24%)
- ✓ E. Minimal change disease (41%)
- F. Poststreptococcal glomerulonephritis (1%)

Incorrect
Correct answer
E

41%
Answered correctly

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Minimal change disease	
Epidemiology	• Most common cause of nephrotic syndrome in children • Median age 2-3
Pathogenesis	• T cell–mediated injury to podocytes • Production of a glomerular permeability factor
Clinical features	• Edema, frothy urine • Proteinuria, hypoalbuminemia, hyperlipidemia
Diagnosis	• LM: normal glomeruli • IM: no immune deposits • EM: diffuse podocyte foot process effacement

EM = electron microscopy; **IM** = immunofluorescence microscopy; **LM** = light microscopy.

This patient with edema, proteinuria, and hypoalbuminemia has nephrotic syndrome. The normal glomeruli on light microscopy (LM) suggest a diagnosis of **minimal change disease** (MCD), the most common cause of nephrotic syndrome in children. It is often idiopathic but may be triggered by drugs (eg, **nonsteroidal anti-inflammatory drugs** [NSAIDs], as in this patient), immunizations, or malignancy (eg, Hodgkin lymphoma).

Pathogenesis involves T cell dysfunction with production of a glomerular permeability factor (possibly IL-13), which damages podocytes and decreases the anionic charge of the glomerular basement membrane (GBM), allowing for selective loss of albumin in the urine.

Clinical features include acute weight gain, diffuse edema, and frothy urine due to heavy proteinuria. Renal biopsy demonstrates **normal glomeruli on LM**, with no immunoglobulin or complement deposits visible on immunofluorescent microscopy. However, electron microscopy shows diffuse effacement and fusion of podocyte foot process.

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This patient with edema, proteinuria, and hypoalbuminemia has nephrotic syndrome. The normal glomeruli on light microscopy (LM) suggest a diagnosis of **minimal change disease** (MCD), the most common cause of nephrotic syndrome in children. It is often idiopathic but may be triggered by drugs (eg, **nonsteroidal anti-inflammatory drugs** [NSAIDs], as in this patient), immunizations, or malignancy (eg, Hodgkin lymphoma).

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(Choice A) Acute interstitial nephritis often occurs after initiation of new drugs (eg, NSAIDS, diuretics) but causes acute kidney injury with white blood cell casts on urinalysis; heavy proteinuria is unexpected. Although the glomeruli are often normal, inflammation involving the interstitium and tubules will be seen on LM.

(Choices B and F) Crescentic glomerulonephritis and poststreptococcal glomerulonephritis cause nephritic syndrome (eg, hematuria, red blood cell casts, hypertension). Crescentic glomerulonephritis occurs in multiple renal diseases (eg, Goodpasture disease, microscopic polyangiitis) and demonstrates hypercellular crescents composed of parietal and inflammatory cells. Poststreptococcal glomerulonephritis, which occurs 2-4 weeks after a group A streptococcal infection, demonstrates hypercellular glomeruli on LM.

(Choice C) Focal segmental glomerulosclerosis causes nephrotic syndrome and also demonstrates similar podocyte foot process effacement on electron microscopy; however, LM demonstrates sclerotic foci within the glomerulus. This disease is more common in adults and typically has a slower onset of edema and weight gain.

(Choice D) Membranous nephropathy causes nephrotic syndrome, and is associated with NSAID use, but is more

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damages podocytes and decreases the anionic charge of the glomerular basement membrane (GBM), allowing for selective loss of albumin in the urine.

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(Choice D) Membranous nephropathy causes nephrotic syndrome, and is associated with NSAID use, but is more common in adults. LM demonstrates glomeruli with diffuse GBM thickening.

Educational objective:
Minimal change disease is the most common cause of nephrotic syndrome in children. It is often idiopathic but may be triggered by drugs, immunizations, or malignancy. Light microscopy shows normal glomeruli, with no immunoglobulin or complement deposits on immunofluorescent staining. However, electron microscopy shows diffuse podocyte foot process effacement and fusion.

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Diagnosis	• IM: no immune deposits • EM: diffuse podocyte foot process effacement

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Nephritic vs nephrotic syndrome

	Nephritic	Nephrotic
Proteinuria	Mild	Significant (>3.5 g/day)
Serum albumin	Normal	Decreased
Edema	Mild	Significant
GFR	Decreased	Normal
Hypertension	Yes	No
Hematuria	Yes	No
Pyuria	Yes	No
Casts	RBC	Fatty or none

GFR = glomerular filtration rate; **RBC** = red blood cell.

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(Choice C) Focal segmental glomerulosclerosis causes nephrotic syndrome and also demonstrates similar podocyte foot process effacement on electron microscopy; however, LM demonstrates sclerotic foci within the

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Diagnosis

- IM: no immune deposits
- EM: diffuse podocyte foot process effacement

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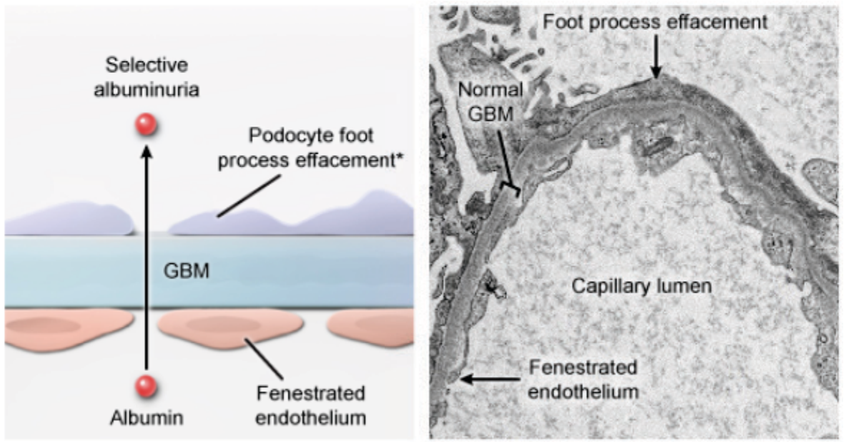
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(Choice C) Focal segmental glomerulosclerosis causes nephrotic syndrome and also demonstrates similar podocyte foot process effacement on electron microscopy; however, LM demonstrates sclerotic foci within the

Minimal change disease



*Retraction & flattening of processes → elongated & flattened cell shape (indicates podocyte injury).
GBM = glomerular basement membrane.
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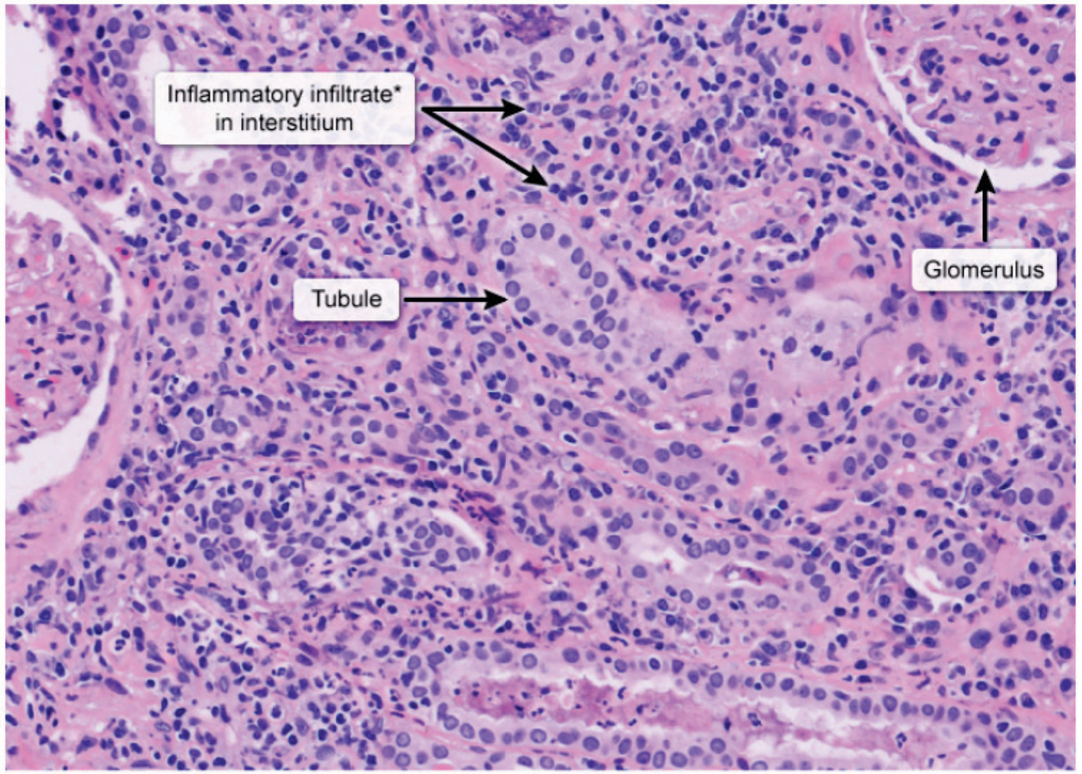
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Diagnosis	• IM: no immune deposits • EM: diffuse podocyte foot process effacement

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Interstitial nephritis



*Predominantly mononuclear cells (eg, lymphocytes).

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(Choice C) Focal segmental glomerulosclerosis causes nephrotic syndrome and also demonstrates similar podocyte foot process effacement on electron microscopy; however, LM demonstrates sclerotic foci within the

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This patient with edema, proteinuria, and hypoalbuminemia has nephrotic syndrome. The normal glomeruli on light micr
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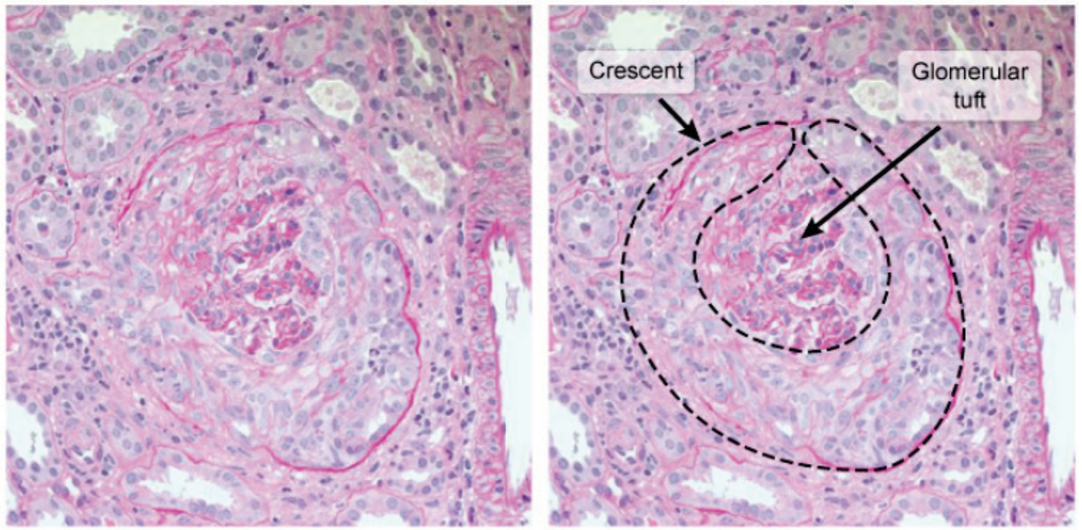
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Crescentic glomerulonephritis



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(Choice D) Membranous nephropathy causes nephrotic syndrome, and is associated with NSAID use, but is more

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drugs [NSAIDs], as in this patient), immunizations, or malignancy (eg, Hodgkin lymphoma).

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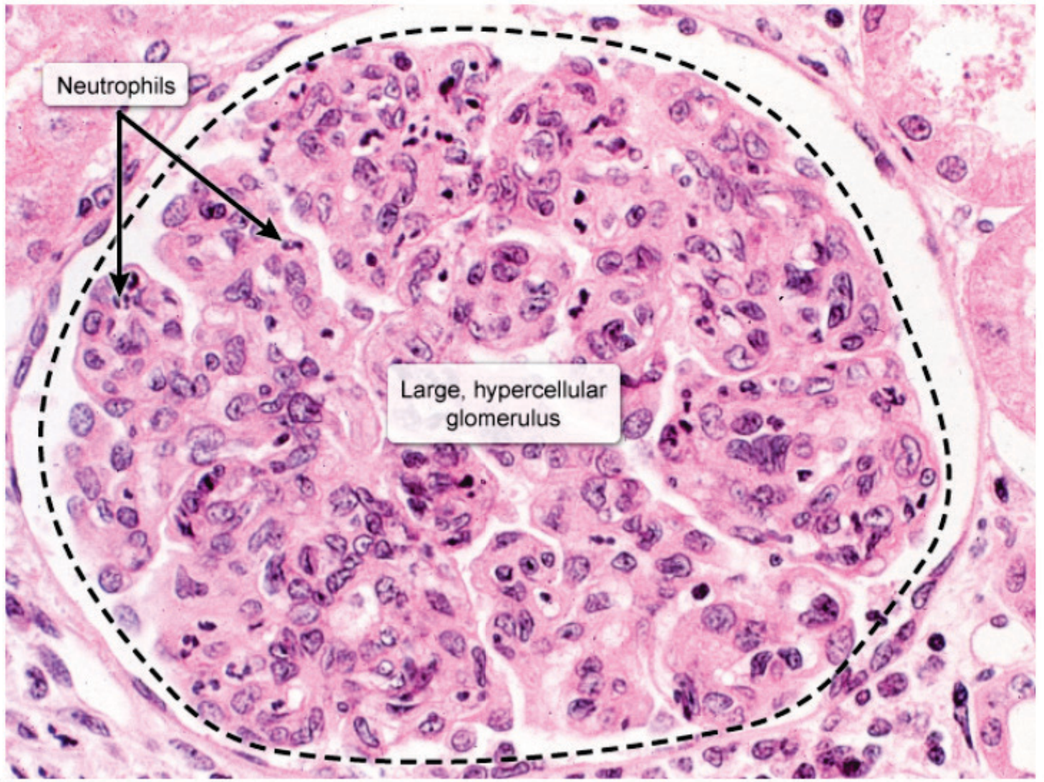
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Minimal change disease is the most common cause of nephrotic syndrome in children. It is often idiopathic but

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Poststreptococcal glomerulonephritis



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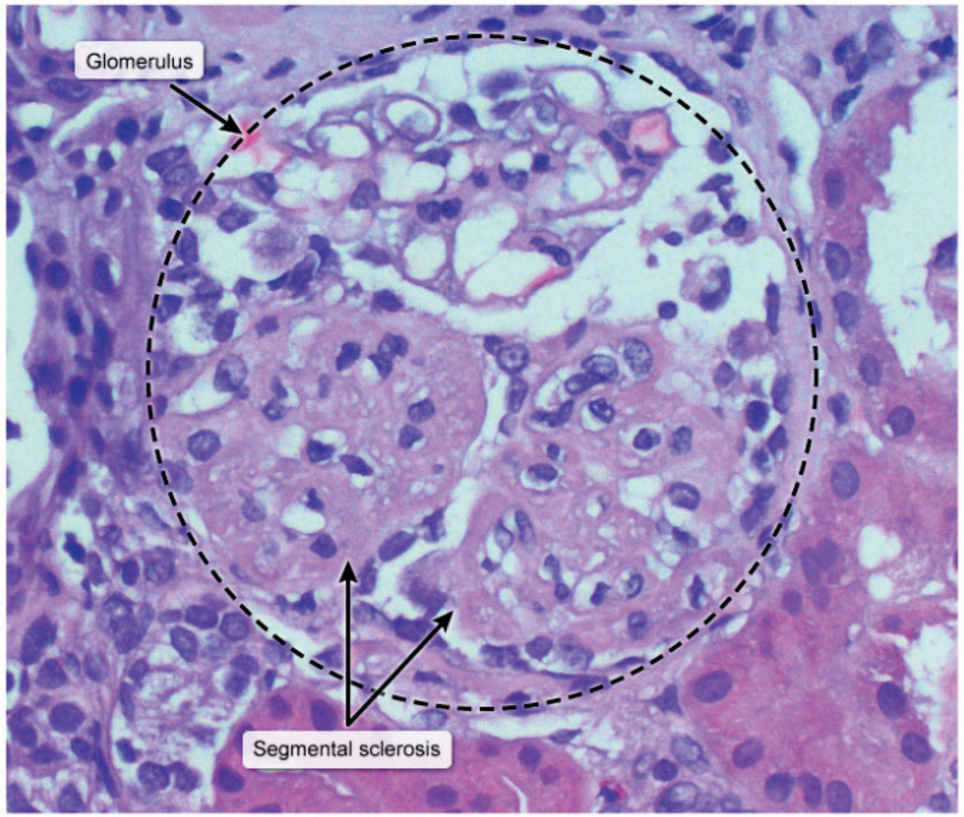
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damages podocytes and decreases the anionic charge of the glomerular basement membrane (GBM), allowing for
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Focal segmental glomerulosclerosis



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A 35-year-old woman comes to the office due to frequent urination. She describes drinking excessive amounts of water due to unquenchable thirst. She does not take any medications. Her blood glucose level is 86 mg/dL. A standard water deprivation test is performed. The results of urine osmolality during 4 hours of dehydration are presented in the table below. The patient's plasma osmolality after 3 hours of water deprivation was found to be 298 mOsm/L, and vasopressin was then administered subcutaneously.

Time (hours)	1	2	3	4
Urine osmolality (mOsm/L)	90	100	100	790

Which of the following is the most likely diagnosis in this patient?

- A. Central diabetes insipidus
- B. Complete nephrogenic diabetes insipidus
- C. Partial nephrogenic diabetes insipidus
- D. Post-obstructive polyuria
- E. Primary polydipsia

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Time (hours)	1	2	3	4
Urine osmolality (mOsm/L)	90	100	100	790

Which of the following is the most likely diagnosis in this patient?

- ✓ A. Central diabetes insipidus (78%)
- ✗ B. Complete nephrogenic diabetes insipidus (5%)
- C. Partial nephrogenic diabetes insipidus (5%)
- D. Post-obstructive polyuria (0%)
- E. Primary polydipsia (9%)

Incorrect
Correct answer
A

78%
Answered correctly

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Explanation

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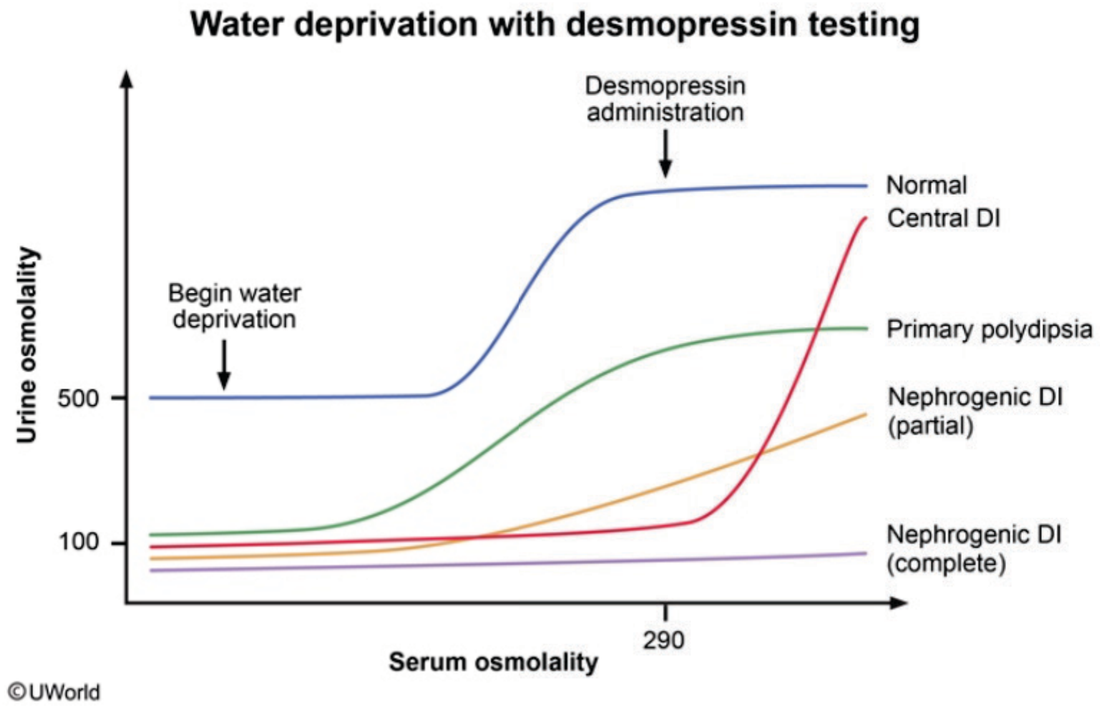
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Diabetes insipidus (DI) is caused by either ADH deficiency (central DI) or complete/partial unresponsiveness of the

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The collecting duct is impermeable to water in the absence of vasopressin (antidiuretic hormone [ADH]). ADH activates G protein-coupled V2 receptors on the basolateral tubular cell membrane, stimulating phosphorylation of intracellular proteins. This causes fusion of vesicles containing aquaporin 2 to the luminal membrane, where aquaporin serves as a water channel and allows water reabsorption in the collecting duct.

Diabetes insipidus (DI) is caused by either ADH deficiency (central DI) or complete/partial unresponsiveness of the kidneys to ADH (nephrogenic DI). The end result is free water loss in the urine with production of dilute urine (low specific gravity and urine osmolality) and dehydration that causes excessive thirst. A water deprivation test with desmopressin (DDAVP) administration can differentiate between central and nephrogenic DI. In patients with central DI and complete nephrogenic DI, the urine osmolality is persistently low despite an increase in serum osmolality with water deprivation. When desmopressin is administered, patients with central DI show a rapid increase in urine osmolality and reduction in urine volume, whereas those with complete nephrogenic DI do not **(Choice B).**

(Choice C) Patients with partial nephrogenic DI have a slow but steady rise in urine osmolality with increasing serum osmolality after water deprivation. There is no further increase in urine osmolality with DDAVP, and the urine osmolality remains low (<500 mOsm/L).

(Choice D) Relief of urinary obstruction (eg, Foley catheterization in patients with benign prostatic hyperplasia) may result in post-obstructive diuresis as the kidneys act to normalize fluid volume and solute levels. It is mostly seen in patients with a history of reduced urine output from chronic urinary obstruction. Urine osmolality remains within normal limits.

(Choice E) Patients with primary polydipsia exhibit an increase in serum and urine osmolality on water deprivation that is similar to partial nephrogenic DI. However, the correction in primary polydipsia is more rapid, and the urine osmolality returns to a level closer to normal (but still submaximal due to washout of the medullary osmotic gradient). A history of psychiatric disorders or medication-induced xerostomia is usually present.

Educational objective:

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aquaporin serves as a water channel and allows water reabsorption in the collecting duct.

Diabetes insipidus (DI) is caused by either ADH deficiency (central DI) or complete/partial unresponsiveness of the kidneys to ADH (nephrogenic DI). The end result is free water loss in the urine with production of dilute urine (low specific gravity and urine osmolality) and dehydration that causes excessive thirst. A water deprivation test with desmopressin (DDAVP) administration can differentiate between central and nephrogenic DI. In patients with central DI and complete nephrogenic DI, the urine osmolality is persistently low despite an increase in serum osmolality with water deprivation. When desmopressin is administered, patients with central DI show a rapid increase in urine osmolality and reduction in urine volume, whereas those with complete nephrogenic DI do not **(Choice B).**

(Choice C) Patients with partial nephrogenic DI have a slow but steady rise in urine osmolality with increasing serum osmolality after water deprivation. There is no further increase in urine osmolality with DDAVP, and the urine osmolality remains low (<500 mOsm/L).

(Choice D) Relief of urinary obstruction (eg, Foley catheterization in patients with benign prostatic hyperplasia) may result in post-obstructive diuresis as the kidneys act to normalize fluid volume and solute levels. It is mostly seen in patients with a history of reduced urine output from chronic urinary obstruction. Urine osmolality remains within normal limits.

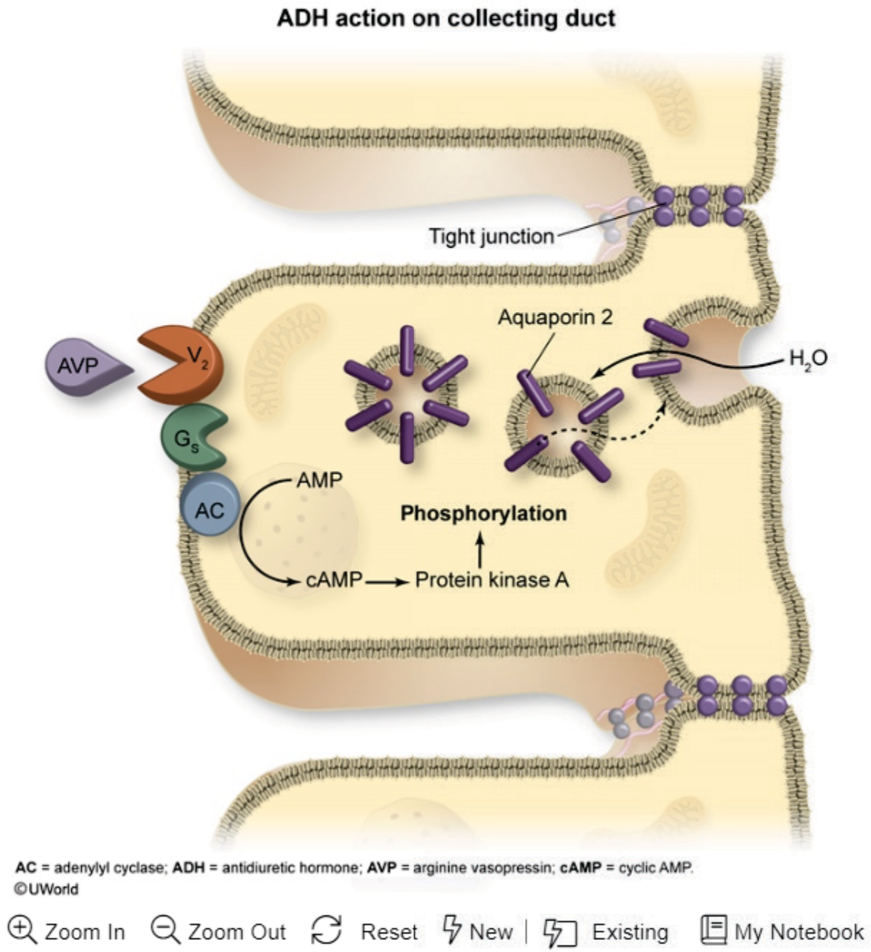
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Educational objective:
Patients with diabetes insipidus (DI) are unable to concentrate their urine in response to dehydration. Following desmopressin administration during the water deprivation test, urine osmolality increases to normal levels in central DI but does not change in complete nephrogenic DI.

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AC = adenylyl cyclase; **ADH** = antidiuretic hormone; **AVP** = arginine vasopressin; **cAMP** = cyclic AMP.
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Causes of diabetes insipidus	
Central	• Pituitary tumors or resection • Head trauma • Primary brain tumors or infiltrative lesions (eg, sarcoidosis, lymphoma) • Brain metastases
Nephrogenic	• Drugs (eg, lithium, amphotericin B, gentamicin, cisplatin) • Hypercalcemia • Hypokalemia • Post obstructive diuresis

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A 6-week-old term boy is brought to the office due to increased fussiness and poor weight gain. The patient has several wet diapers per day. His anterior fontanelle is flat and mucous membranes are dry. Laboratory results include the following:

Sodium	148 mEq/L
Potassium	3.5 mEq/L
Antidiuretic hormone	increased

Urinalysis shows a specific gravity of 1.002. Which of the following is the most appropriate treatment for this patient's condition?

- A. Desmopressin
- B. Hydrochlorothiazide
- C. Hydrocortisone
- D. Insulin
- E. Salt tablets

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Sodium	148 mEq/L
Potassium	3.5 mEq/L
Antidiuretic hormone	increased

Urinalysis shows a specific gravity of 1.002. Which of the following is the most appropriate treatment for this patient's condition?

- ✗ A. Desmopressin (25%)
- ✓ B. Hydrochlorothiazide (49%)
- C. Hydrocortisone (11%)
- D. Insulin (7%)
- E. Salt tablets (6%)

Incorrect
Correct answer
B

49%
Answered correctly

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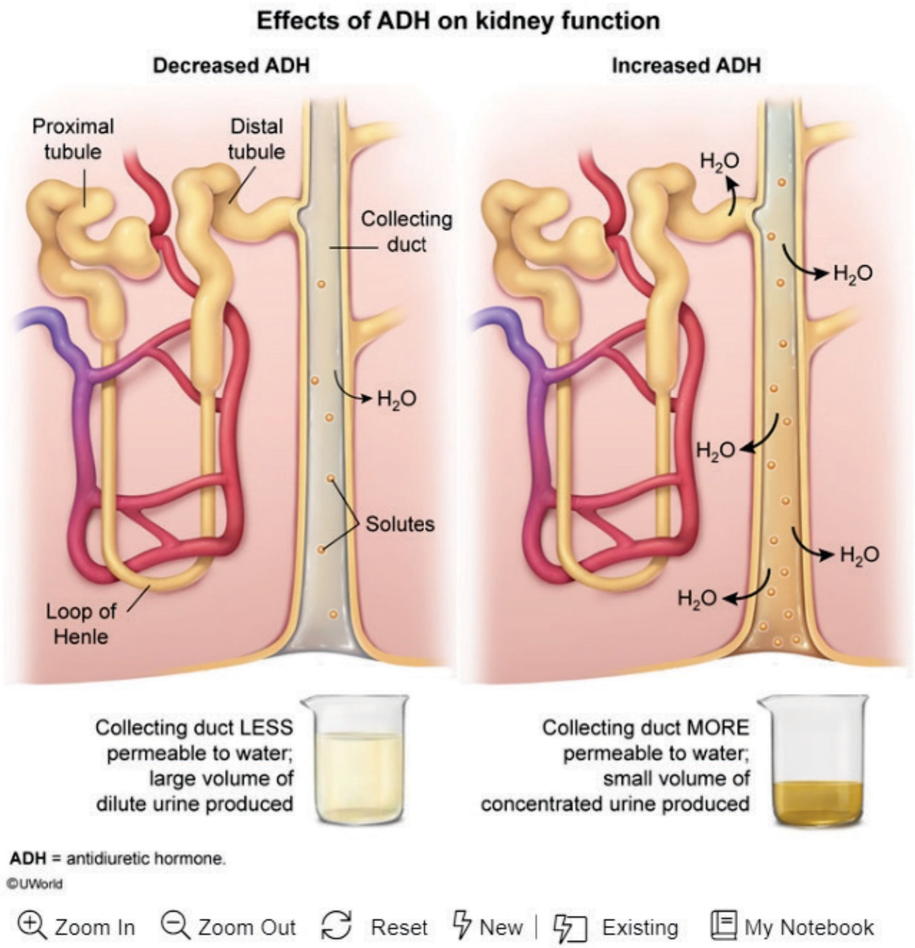
Explanation

Effects of ADH on kidney function

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D. Insulin (7%)

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This **dehydrated infant** (eg, flat fontanelle, dry mucous membranes, hypernatremia) is inappropriately producing **dilute urine** (eg, low urine specific gravity [<1.006]) **in large quantities** (eg, several wet diapers daily) despite having **high levels of ADH**, which is consistent with **nephrogenic diabetes insipidus (NDI)**. NDI is caused by resistance to **antidiuretic hormone** (ADH, or vasopressin) within the renal collecting ducts. Although NDI in adults is commonly due to medications (eg, lithium), in children, it is typically due to congenital mutations involving the vasopressin (V2) receptor or aquaporin 2 channel.

ADH is secreted when serum osmolality is high (eg, water deprivation) or extracellular volume is low (eg, dehydration). Normally, ADH increases water reabsorption in the renal collecting ducts, which increases urinary concentration (eg, high urine osmolality and specific gravity) and lowers serum sodium, serum osmolality, and urinary volume.

Infants with NDI cannot freely replace ongoing water losses, and early diagnosis and treatment is essential for preventing associated mental and physical growth retardation. Treatment aims to minimize urinary water loss and includes **frequent water supplementation** and, paradoxically, **thiazide administration** (eg, hydrochlorothiazide). Thiazides appear to **reduce renal water losses** in NDI by inducing a mild volume depletion that increases sodium and water reabsorption in the proximal tubule. This decreases the total amount of water delivered to the collecting ducts, allowing for better retention of supplemental water.

(Choice A) Desmopressin (an ADH analog) is used to treat central diabetes insipidus, a disorder caused by deficient ADH secretion by the hypothalamus and posterior pituitary. Central diabetes insipidus is associated with low, rather than high, ADH levels.

(Choice C) Hydrocortisone can be used to treat adrenal insufficiency, which may also present with hypovolemia and high ADH levels. However, renal ADH response is intact; therefore, hyponatremia and high urine specific gravity would be expected

(Choice D) Severe hyperglycemia from diabetes mellitus can lead to polyuria and dehydration; however,

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concentration (eg, high urine osmolality and specific gravity) and lowers serum sodium, serum osmolality, and urinary volume.

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(Choice C) Hydrocortisone can be used to treat adrenal insufficiency, which may also present with hypovolemia and high ADH levels. However, renal ADH response is intact; therefore, hyponatremia and high urine specific gravity would be expected

(Choice D) Severe hyperglycemia from diabetes mellitus can lead to polyuria and dehydration; however, increased urinary glucose would cause high urine specific gravity and urine osmolality.

(Choice E) Salt tablets can treat the syndrome of inappropriate ADH, which is associated with hyponatremia and high urine specific gravity.

Educational objective:
Nephrogenic diabetes insipidus is characterized by polyuria, dilute urine (low urine specific gravity), hypernatremia, and high antidiuretic hormone. Treatment includes thiazide diuretics and replacement of water losses.

References

- Paradoxical antidiuretic effect of thiazides in diabetes insipidus: another piece in the puzzle.

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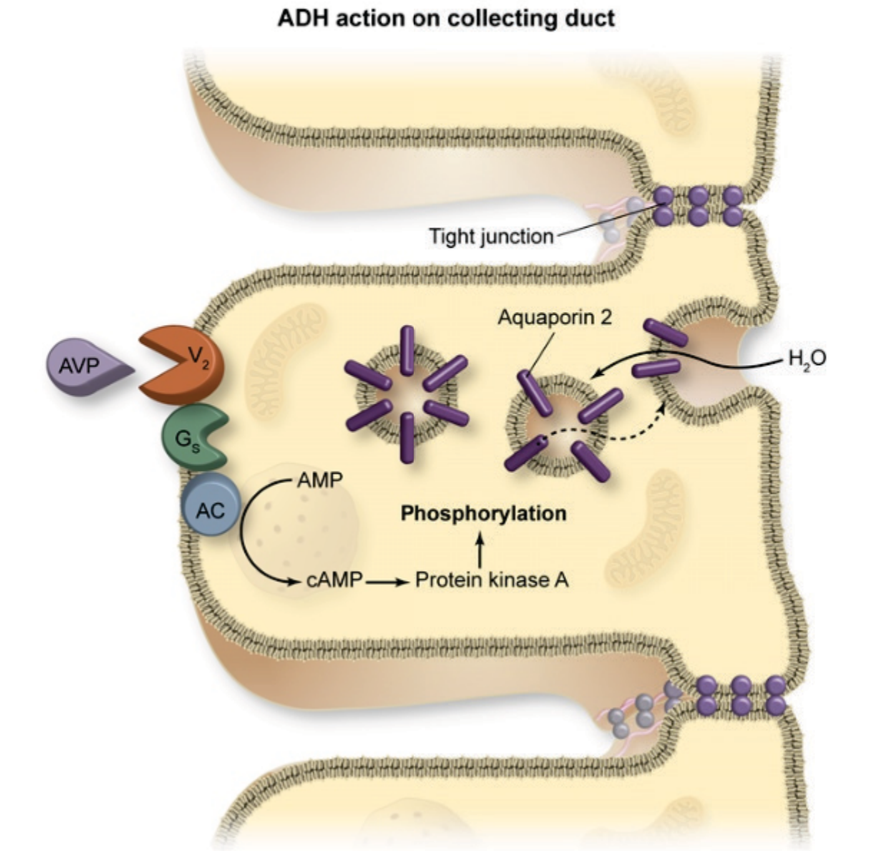
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AC = adenylyl cyclase; **ADH** = antidiuretic hormone; **AVP** = arginine vasopressin; **cAMP** = cyclic AMP.
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(Choice D) Severe hyperglycemia from diabetes mellitus can lead to polyuria and dehydration; however,

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A 24-year-old man who lives at an elevation near sea-level goes on a multiday hiking trip in the Colorado mountains and ascends to an altitude of 4,000 m (13,123 ft). Over the next 3 days, the patient develops diffuse headaches, nausea, and difficulty sleeping. The patient also notes mild fatigue and slight dizziness with changes in position. He has no medical conditions and takes no medications. He does not use alcohol, tobacco, or illicit drugs. Which of the following changes in this patient's acid-base physiology is most likely to be seen?

	Arterial pH	Renal H^+ secretion	Renal HCO_3^- reabsorption
○ A.	↓	↑	↓
○ B.	↑	↓	↓
○ C.	↑	No change	↓
○ D.	No change	↓	↓
○ E.	↓	↓	↑
○ F.	↑	↑	No change

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	Arterial pH	Renal H^+ secretion	Renal HCO_3^- reabsorption	
A.	↓	↑	↓	(10%)
✓ B.	↑	↓	↓	(48%)
✗ C.	↑	No change	↓	(15%)
D.	No change	↓	↓	(2%)
E.	↓	↓	↑	(13%)
F.	↑	↑	No change	(9%)

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Correct answer
B

48%
Answered correctly

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Explanation

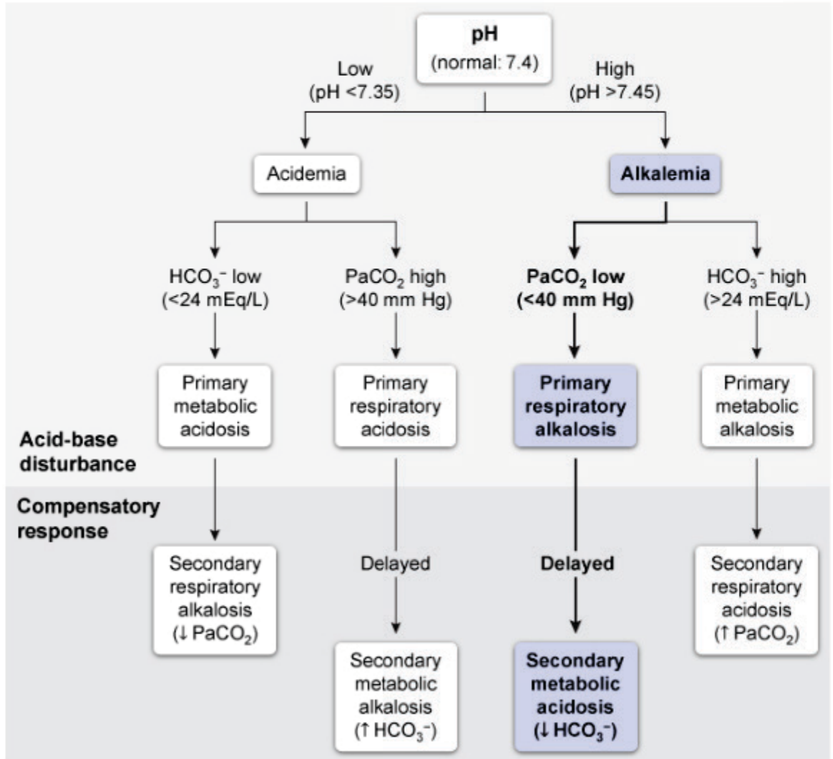
Arterial blood gas interpretation of acid-base disorders

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C. ↑ No change ↓ (15%)

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Arterial blood gas interpretation of acid-base disorders



* The normal ranges for $PaCO_2$ and HCO_3^- vary slightly around 40 mm Hg and 24 mEq/L.
For simplicity, these numbers should be used as a normal baseline for acid-base calculations.

HCO_3^- = bicarbonate; **$PaCO_2$** = partial pressure of carbon dioxide in arterial blood.

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disturbance

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At **high altitude**, the low barometric pressure decreases the partial pressure of inspired oxygen (PiO_2) and leads to **hypoxemia**, which in turn triggers a chemoreceptor-mediated increase in respiratory drive with resulting hyperventilation. An unwanted effect of the hyperventilation is excessive expiration of CO_2, leading to **respiratory alkalosis** and increased blood pH **(Choices A, D, and E)**. The hypoxemia and alkalemia can cause **altitude sickness**, which presents with headache, fatigue, lightheadedness, nausea, and insomnia.

Over time, the body makes physiologic adjustments to better tolerate high altitude:

- In response to respiratory alkalosis, the **kidneys decrease HCO_3^- reabsorption** and **H^+ secretion** to create a compensatory metabolic acidosis (a process that begins within 6-12 hours and requires several days to complete) **(Choices C and F)**.
- Alkalosis also causes a left shift in the hemoglobin dissociation curve, which initially impairs tissue oxygen delivery; however, the curve is shifted back to the right by increased production of 2,3-biphosphoglycerate in red blood cells, facilitating O_2 unloading in the tissues.
- Chronic hypoxemia triggers increased erythropoietin secretion by the kidneys with a resulting increase in red blood cell production (a process that requires several weeks).

On initial exposure to high altitude, the administration of a carbonic anhydrase inhibitor (eg, **acetazolamide**) can accelerate the loss of HCO_3^- by the kidneys to help relieve the alkalemia and treat altitude sickness.

Educational objective:
At high altitude, the low partial pressure of inspired oxygen (PiO_2) leads to hypoxemia with consequent hyperventilation and respiratory alkalosis. The hypoxemia and alkalemia can cause symptoms of altitude sickness (eg, headache, fatigue, lightheadedness). The kidneys respond by creating a compensatory metabolic acidosis and by increasing erythropoietin secretion.

References

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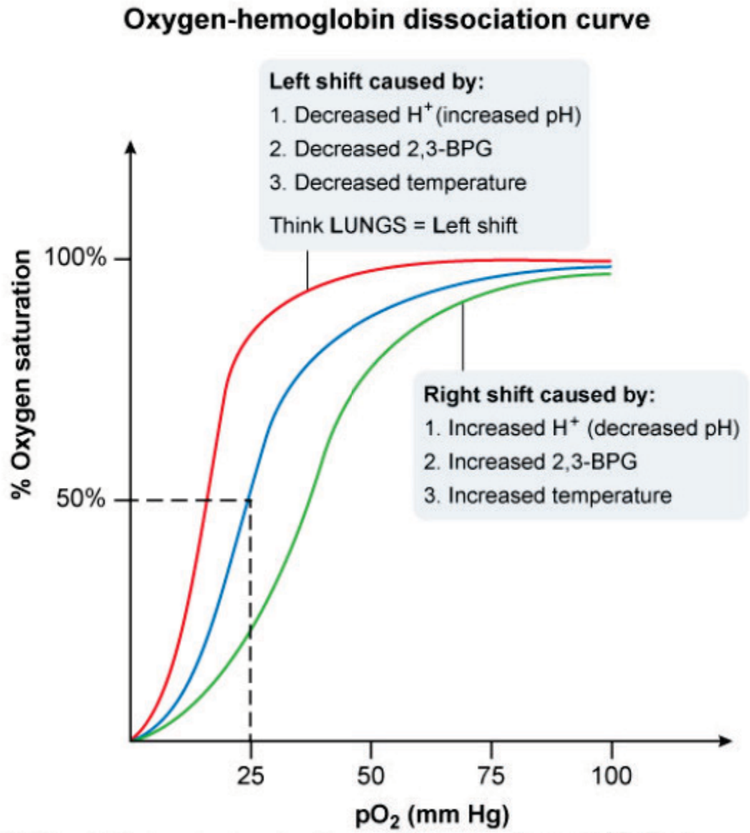
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References

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2,3-BPG = 2,3-bisphosphoglycerate; **pO_2** = partial pressure of oxygen in the blood.

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A 42-year-old man comes to the office due to hematuria, fatigue, and nasal congestion for the last few weeks. He has no chronic medical conditions. Blood pressure is 160/96 mm Hg. Physical examination shows edema around the ankles, hands, and face. Laboratory results reveal blood urea nitrogen of 40 mg/dL and serum creatinine of 3.8 mg/dL. Urinalysis shows moderate proteinuria and a large amount of red blood cells (RBCs) with RBC casts. A kidney biopsy is performed. Light microscopy reveals cellular proliferation, focal necrosis, and crescent formation of most of the glomeruli. On immunofluorescent microscopy, there are no immunoglobulin or complement deposits. Which of the following additional findings is most likely to be present in this patient?

- A. Decreased serum C3 level
- B. Decreased serum C4 level
- C. Serum antiglomerular basement membrane antibodies
- D. Serum antineutrophil cytoplasmic antibodies
- E. Serum antiphospholipid antibodies

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- A. Decreased serum C3 level (12%)
- ✗ B. Decreased serum C4 level (1%)
- C. Serum antiglomerular basement membrane antibodies (18%)
- ✓ D. Serum antineutrophil cytoplasmic antibodies (64%)
- E. Serum antiphospholipid antibodies (3%)

Incorrect
Correct answer
D

64%
Answered correctly

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Time Spent

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Explanation

Crescent formation on light microscopy is diagnostic of **rapidly progressive (crescentic) glomerulonephritis** (RPGN). This is a syndrome of severe glomerular injury that rapidly progresses to renal failure within weeks to months of onset. RPGN can be caused by several different diseases and is classified based on immunologic findings:

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Explanation

Crescent formation on light microscopy is diagnostic of **rapidly progressive (crescentic) glomerulonephritis** (RPGN). This is a syndrome of severe glomerular injury that rapidly progresses to renal failure within weeks to months of onset. RPGN can be caused by several different diseases and is classified based on immunologic findings:

- **Antiglomerular basement membrane (anti-GBM) RPGN:** Linear GBM deposits of IgG and C3 are found on immunofluorescence **(Choice C)**. In some patients, anti-GBM antibodies cross-react with pulmonary alveolar basement membranes, producing pulmonary hemorrhages (Goodpasture syndrome).
- **Immune-complex RPGN:** There is a "lumpy-bumpy" granular pattern of staining for both antibodies (eg, IgG, IgA) and complement on immunofluorescence microscopy. This can be a complication of poststreptococcal glomerulonephritis, systemic lupus erythematosus, IgA nephropathy, or Henoch-Schönlein purpura.
- **Pauci-immune RPGN:** There are **no immunoglobulin or complement deposits** on the basement membrane, as with this patient. Most patients have elevated serum titers of **antineutrophil cytoplasmic antibodies** (ANCA). This condition is often associated with vasculitides (eg, granulomatosis with polyangiitis, microscopic polyangiitis) but can also be idiopathic.

(Choices A and B) Serum C3 and C4 levels are usually normal with pauci-immune RPGN. Decreased serum C3 or C4 levels often occur in diseases with prominent immune complex formation, such as poststreptococcal glomerulonephritis, systemic lupus erythematosus (which causes immune-complex RPGN), and membranoproliferative glomerulonephritis.

(Choice E) Serum antiphospholipid antibodies are detected in patients with autoimmune disorders such as systemic lupus erythematosus and antiphospholipid syndrome. Antiphospholipid antibodies are associated with venous and arterial thrombosis, not crescent formation.

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findings:

- **Antiglomerular basement membrane (anti-GBM) RPGN:** Linear GBM deposits of IgG and C3 are found on immunofluorescence **(Choice C)**. In some patients, anti-GBM antibodies cross-react with pulmonary alveolar basement membranes, producing pulmonary hemorrhages (Goodpasture syndrome).
- **Immune-complex RPGN:** There is a "lumpy-bumpy" granular pattern of staining for both antibodies (eg, IgG, IgA) and complement on immunofluorescence microscopy. This can be a complication of poststreptococcal glomerulonephritis, systemic lupus erythematosus, IgA nephropathy, or Henoch-Schönlein purpura.
- **Pauci-immune RPGN:** There are **no immunoglobulin or complement deposits** on the basement membrane, as with this patient. Most patients have elevated serum titers of **antineutrophil cytoplasmic antibodies** (ANCA). This condition is often associated with vasculitides (eg, granulomatosis with polyangiitis, microscopic polyangiitis) but can also be idiopathic.

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(Choice E) Serum antiphospholipid antibodies are detected in patients with autoimmune disorders such as systemic lupus erythematosus and antiphospholipid syndrome. Antiphospholipid antibodies are associated with venous and arterial thrombosis, not crescent formation.

Educational objective:
Pauci-immune rapidly progressive glomerulonephritis frequently occurs as a manifestation of antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (eg, granulomatosis with polyangiitis, microscopic polyangiitis). It is characterized by glomerular crescent formation without immunoglobulin or complement deposits.

Pathology Renal, Urinary Systems & Electrolytes Granulomatosis with polyangiitis

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A 1 week-old boy is evaluated in the hospital. The patient has been admitted due to urosepsis and is receiving antibiotic therapy. The mother received no prenatal care; the neonate was born at term via spontaneous vaginal delivery. Vital signs are normal. Examination shows lower abdominal distension with normal bowel sounds. The penis and scrotum appear normal. Renal ultrasonography and voiding cystourethrography reveal a diffusely thickened bladder wall with bilateral vesicoureteral reflux and hydronephrosis. Which of the following is the most likely cause of this patient's findings?

- A. Congenitally short intravesical ureters
- B. Failed obliteration of the allantois
- C. Fusion of the bilateral metanephros
- D. Persistence of the urogenital membrane
- E. Stenosis at the ureteropelvic junction

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- A. Congenitally short intravesical ureters (16%)
- ✗ B. Failed obliteration of the allantois (5%)
- C. Fusion of the bilateral metanephros (8%)
- ✓ D. Persistence of the urogenital membrane (40%)
- E. Stenosis at the ureteropelvic junction (28%)

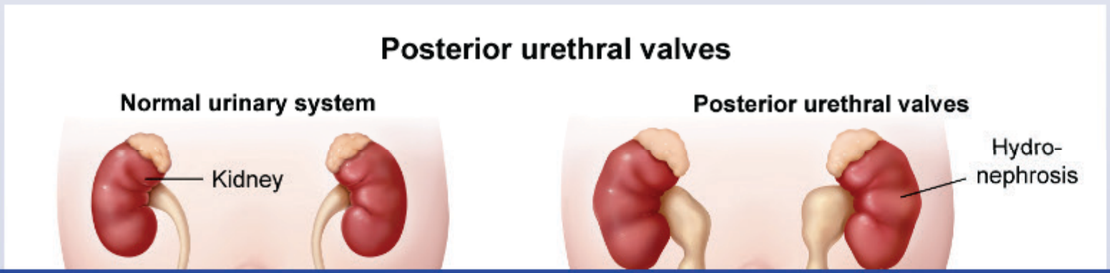
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Correct answer
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Answered correctly

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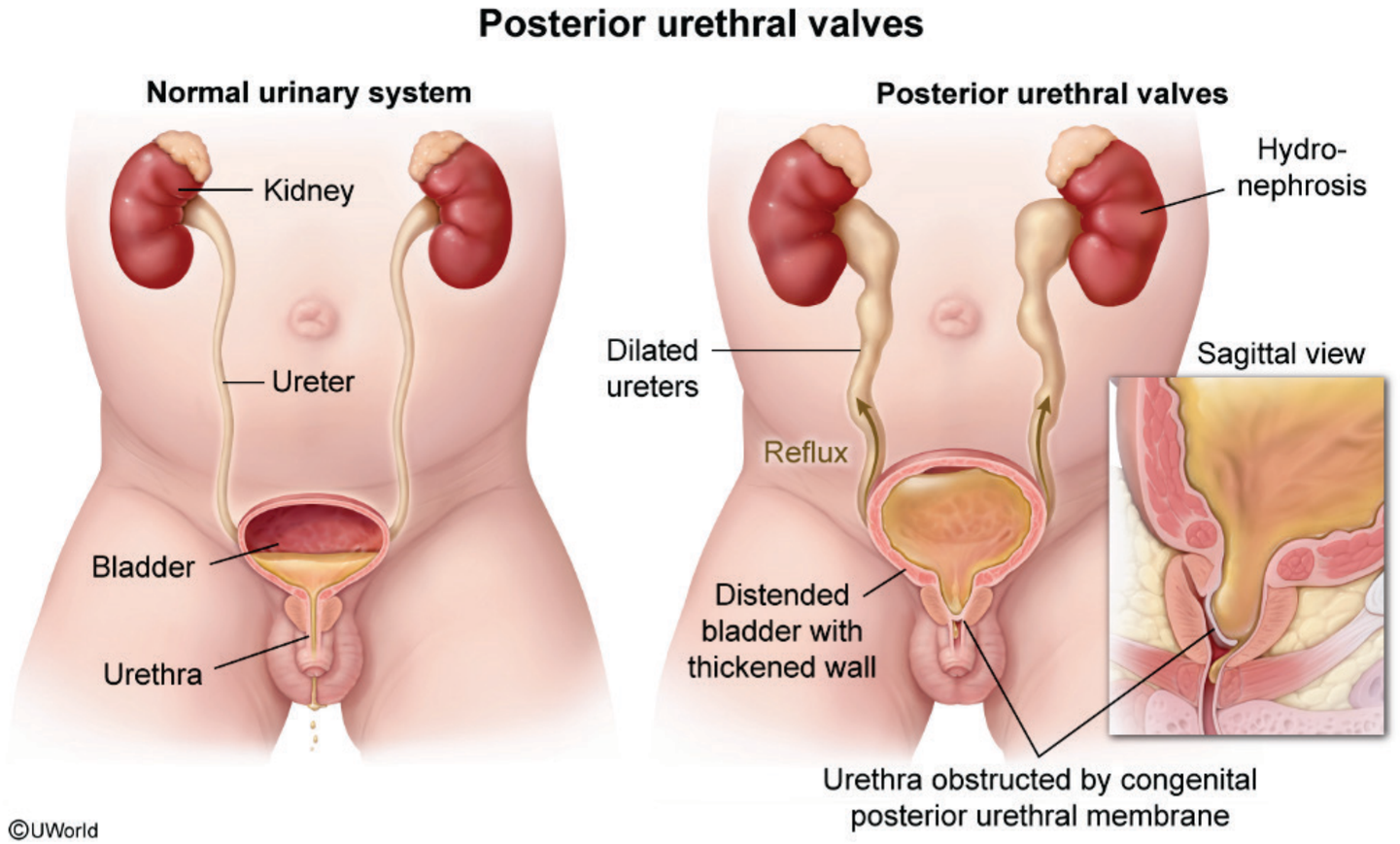
Explanation



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Explanation

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- **Bladder distension** with an increased contractile force required to overcome the obstruction, resulting in

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This patient has a diffusely thickened bladder wall with bilateral vesicoureteral reflux and hydronephrosis, findings consistent with bladder outlet obstruction. In newborn **boys**, the most common cause is **posterior urethral valves** (PUVs).

In utero, the urethra normally begins as a solid structure that canalizes to form its characteristic tubular structure. PUVs are likely due to incomplete canalization and are defined by a **persistent urogenital membrane** that obstructs the posterior urethra. The bladder outlet obstruction, which may be partial or complete, causes increased pressure in the proximal urinary tract, leading to the following:

- **Bladder distension** with an increased contractile force required to overcome the obstruction, resulting in detrusor muscle hypertrophy and bladder **wall thickening**
- Bilateral secondary **vesicoureteral reflux** due to higher pressure in the bladder relative to the ureters and **hydronephrosis** due to retrograde urine flow

Diagnosis is often made via prenatal ultrasound, which may show oligohydramnios if the obstruction is severe. PUVs diagnosed after birth often present with lower abdominal distension, weak urinary stream (if the obstruction is partial), or urinary tract infection (UTI) due to urinary stasis and reflux.

(Choice A) Primary vesicoureteral reflux is due to a congenitally short intravesical ureter that fails to fully compress during micturition, causing retrograde urine flow. Ureteral dilation, hydronephrosis, and UTIs may develop, but the bladder is distal to the defect and would not be distended or have a thickened wall.

(Choice B) Failed obliteration of the allantois leads to a patent urachus, or a connection between the bladder and umbilicus. The risk for UTI is increased, but drainage of urine through the umbilicus is typical and urinary obstruction is not seen.

(Choices C and E) Fusion of the bilateral metanephros (metanephric blastema) causes horseshoe kidney. This condition increases the risk for UTIs, as well as hydronephrosis due to potential ureteropelvic junction (UPJ) obstruction, but the kidneys would be fused on imaging. Moreover, the bladder (distal to the defect) would not be

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In utero, the urethra normally begins as a solid structure that canalizes to form its characteristic tubular structure. PUVs are likely due to incomplete canalization and are defined by a **persistent urogenital membrane** that obstructs the posterior urethra. The bladder outlet obstruction, which may be partial or complete, causes increased pressure in the proximal urinary tract, leading to the following:

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Educational objective:

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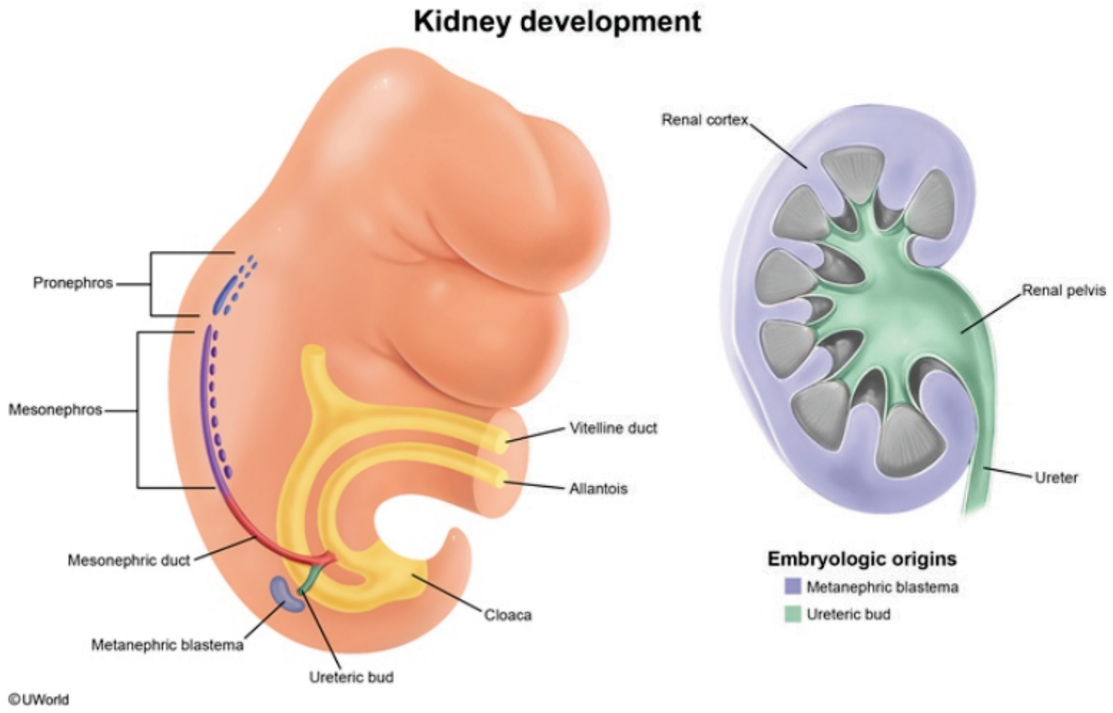
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Educational objective:
Bladder outlet obstruction leads to increased pressure proximally and findings of bladder distension and wall thickening, secondary vesicoureteral reflux, ureteral dilation, and hydronephrosis. The most common cause in newborn boys is posterior urethral valves due to a persistent urogenital membrane.

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detrusor muscle hypertrophy and bladder **wall thickening**

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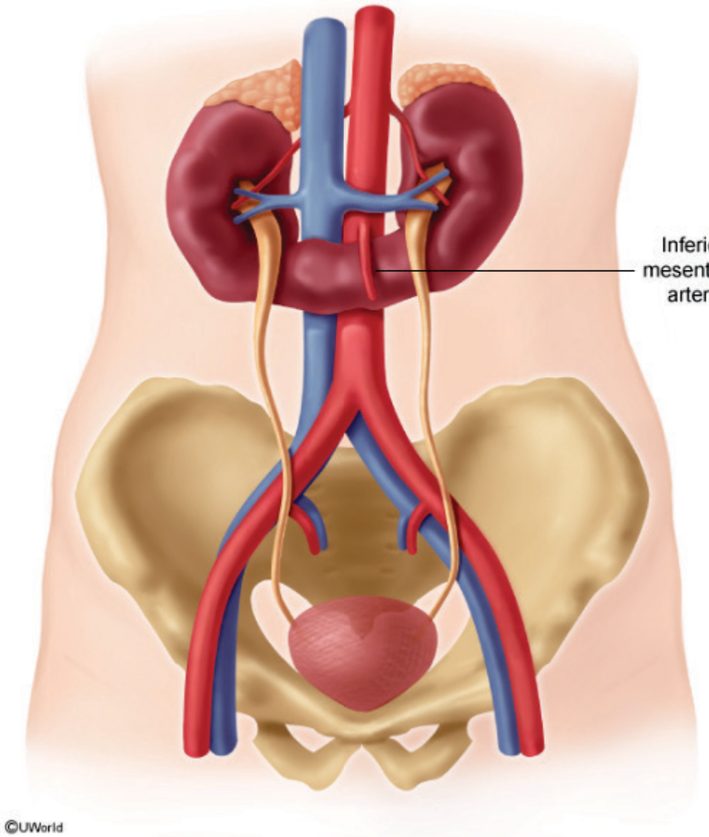


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detrusor muscle hypertrophy and bladder **wall thickening**

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Horseshoe kidney



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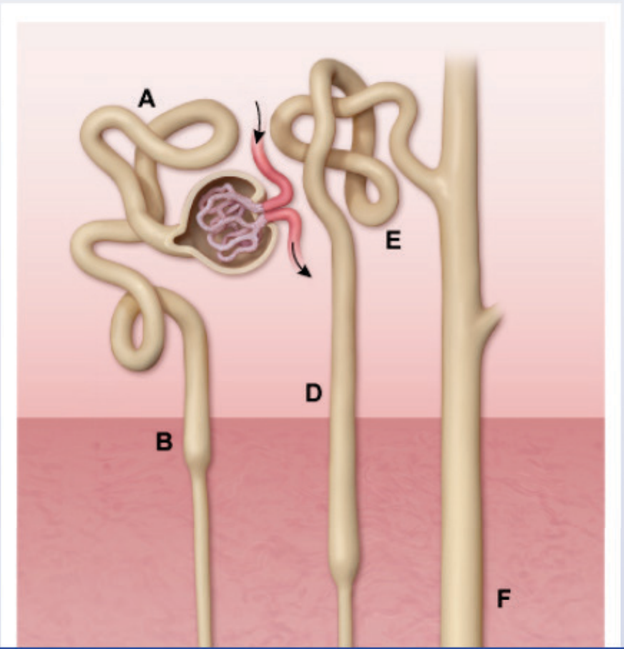
- C

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A 35-year-old woman who is being treated for bipolar disorder complains of excessive thirst and frequent urination. She awakens 3-4 times nightly to void. A urinalysis performed after 8 hours of nothing to eat or drink shows the following:

Specific gravity	1.005 (normal: 1.003-1.030)
Glucose	Negative
Protein	Negative
Ketones	Trace

Which of the following parts of the nephron is most likely impaired in this patient?

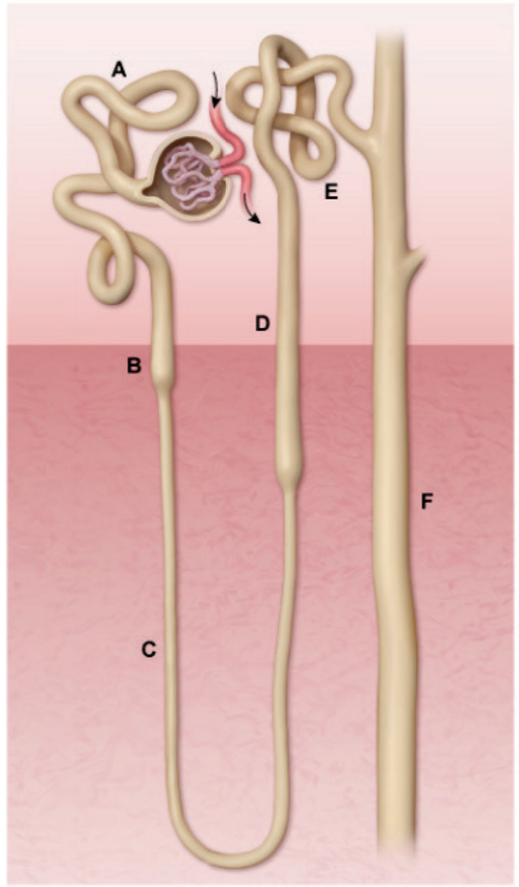


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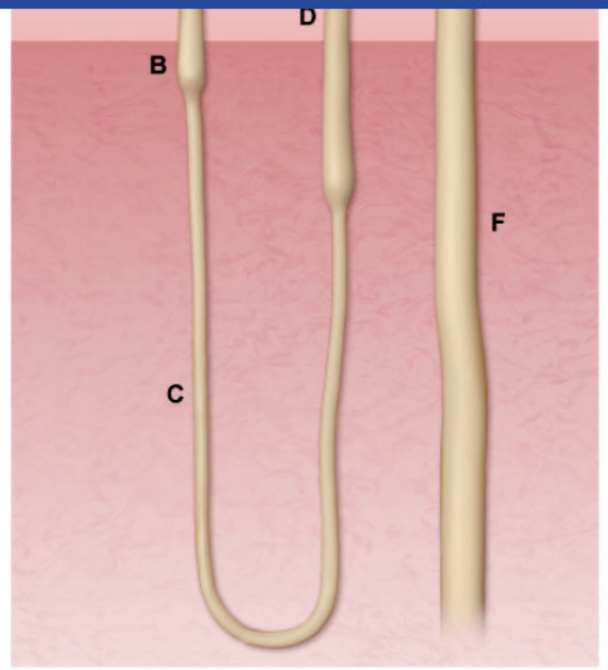
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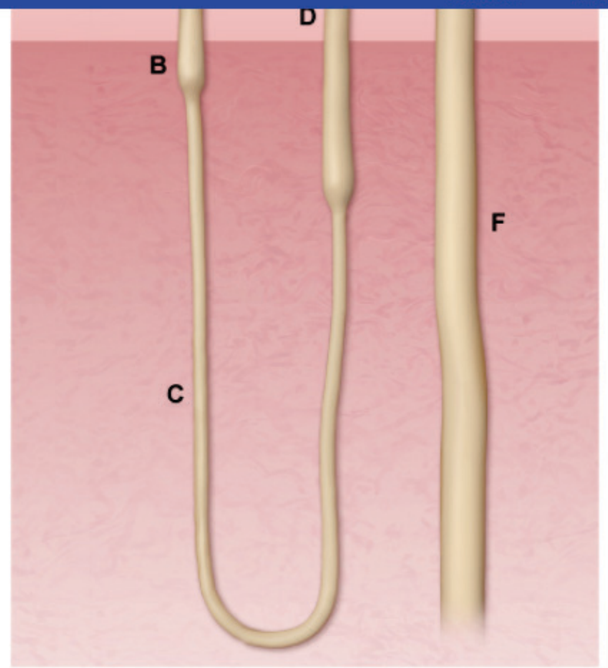
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- A. A
- B. B
- C. C
- D. D
- E. E
- F. F

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- ✗ A. A (10%)
- B. B (1%)
- C. C (2%)
- D. D (2%)
- E. E (7%)
- ✓ F. F (75%)

Incorrect
Correct answer
F

75%
Answered correctly

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This patient presents with polydipsia, polyuria, and an inappropriately **low urine specific gravity** after 8 hours of water restriction. Although within the normal range, specific gravity should be higher after water deprivation (ie, > 1.010), reflecting concentrated urine.

Given her **psychiatric history**, these findings are highly suggestive of lithium-induced nephrogenic **diabetes insipidus**. Therapy with **lithium** reduces the ability of the kidneys to concentrate urine primarily by **antagonizing the action of vasopressin** (antidiuretic hormone) in the **collecting tubules and ducts**. Nephrogenic diabetes insipidus caused by lithium usually resolves following discontinuation of the drug. However, impairment can be permanent following years of chronic use.

(Choice A) The proximal tubule is the site of action of carbonic anhydrase inhibitors.

(Choices B and C) Osmotic diuretics such as mannitol function mainly in the proximal tubule and the descending limb of the loop of Henle.

(Choice D) The thick ascending limb of the loop of Henle is the site of action of loop diuretics such as furosemide.

(Choice E) The early distal convoluted tubule is the site of action of thiazide diuretics.

Educational objective:
Lithium-induced diabetes insipidus is the result of lithium's antagonizing effect on the action of vasopressin on principal cells within the collecting duct system.

References

- Lithium: a versatile tool for understanding renal physiology.

Pharmacology	Renal, Urinary Systems & Electrolytes	Lithium
Subject	System	Topic

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A 45-year-old man is evaluated for a progressively enlarging neck mass and hoarseness. Physical examination shows an enlarged and nontender left thyroid lobe. Fine-needle aspiration biopsy is positive for papillary thyroid cancer, and a thyroidectomy is subsequently performed. On the second postoperative day, the patient develops tingling around the mouth and muscle cramps in his lower extremities. Blood pressure is 120/80 mm Hg, pulse is 82/min, and respirations are 14/min. Physical examination shows normal muscle strength and deep tendon reflexes. Light tapping anterior to the ear elicits twitching of the lower facial muscles. An increase in which of the following best explains this patient's current symptoms?

- A. Calcium binding by albumin
- B. Calcium release from bones
- C. Hydroxylation of vitamin D
- D. Intestinal phosphate absorption
- E. Urinary calcium excretion

Submit

https://t.me/USMLEWorldStep1

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- A. Calcium binding by albumin (8%)
- ✗ B. Calcium release from bones (11%)
- C. Hydroxylation of vitamin D (2%)
- D. Intestinal phosphate absorption (7%)
- ✓ E. Urinary calcium excretion (70%)

Incorrect
Correct answer
E

70%
Answered correctly

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Time Spent

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Version

Explanation

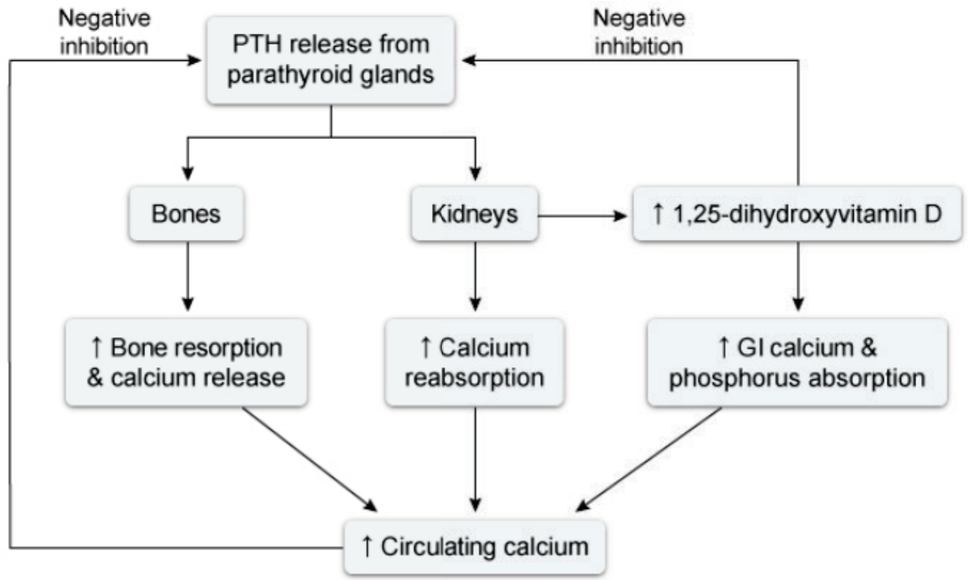


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D. Intestinal phosphate absorption (7%)

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Parathyroid hormone, vitamin D & calcium axis



GI = gastrointestinal; **PTH** = parathyroid hormone.

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This patient has perioral paresthesias and a positive Chvostek sign, which are typical manifestations of acute

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This patient has perioral paresthesias and a positive Chvostek sign, which are typical manifestations of acute **hypocalcemia**. Hypocalcemia is a common complication of thyroid surgery due to iatrogenic injury (eg, devascularization, inadvertent removal) to the parathyroid glands and subsequent **hypoparathyroidism**.

Calcium and phosphate homeostasis is regulated by 2 primary hormones: **parathyroid hormone** (PTH), which regulates minute-to-minute concentrations, and **vitamin D**, which regulates levels over the longer term. PTH is a polypeptide hormone that is produced by the chief cells of the parathyroid glands in response to hypocalcemia and has 3 primary effects:

- Increases osteoclastic **bone resorption**, which releases calcium and phosphate into the circulation
- Increases **renal calcium reabsorption** and reduces phosphate reabsorption
- Increases formation of **1,25-dihydroxyvitamin D** (by upregulating renal 1-alpha-hydroxylase), which increases intestinal calcium absorption

Acute hypoparathyroidism results in decreased calcium and phosphate release from bone **(Choice B)** and **decreased calcium reabsorption** by the kidneys. Inadequate PTH also reduces phosphate excretion by the kidneys and decreases the hydroxylation of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (the more active form) in the renal tubular cells **(Choice C)**. This, in turn, decreases intestinal absorption of calcium and phosphate **(Choice D)**.

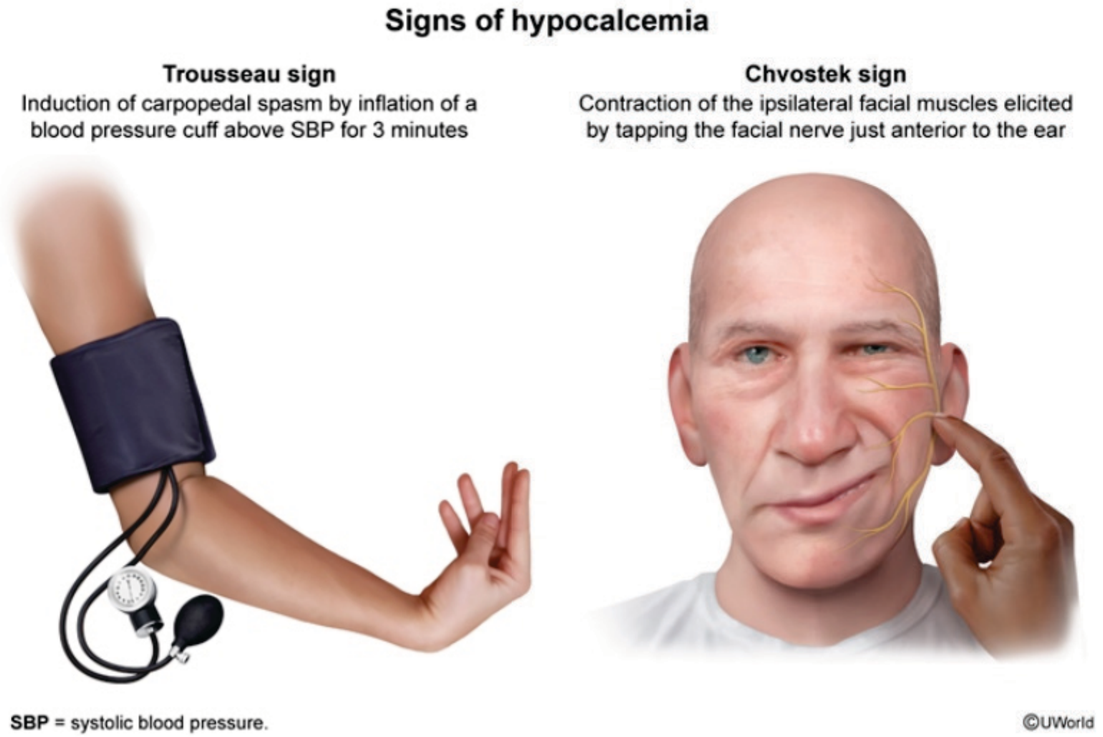
(Choice A) Elevated plasma pH enhances the binding of calcium to albumin, which leading to a precipitous drop in ionized calcium concentration that can induce symptoms of hypocalcemia. However, this patient has no indication of a respiratory (eg, tachypnea) or metabolic (eg, vomiting, hypovolemia) alkalosis.

Educational objective:
Postoperative hypocalcemia is common after thyroid surgery, due to inadvertent removal or damage to the parathyroid glands. The acute drop in parathyroid hormone level results in decreased calcium and phosphate resorption from bone and decreased calcium reabsorption by the kidneys.

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↑ Circulating calcium

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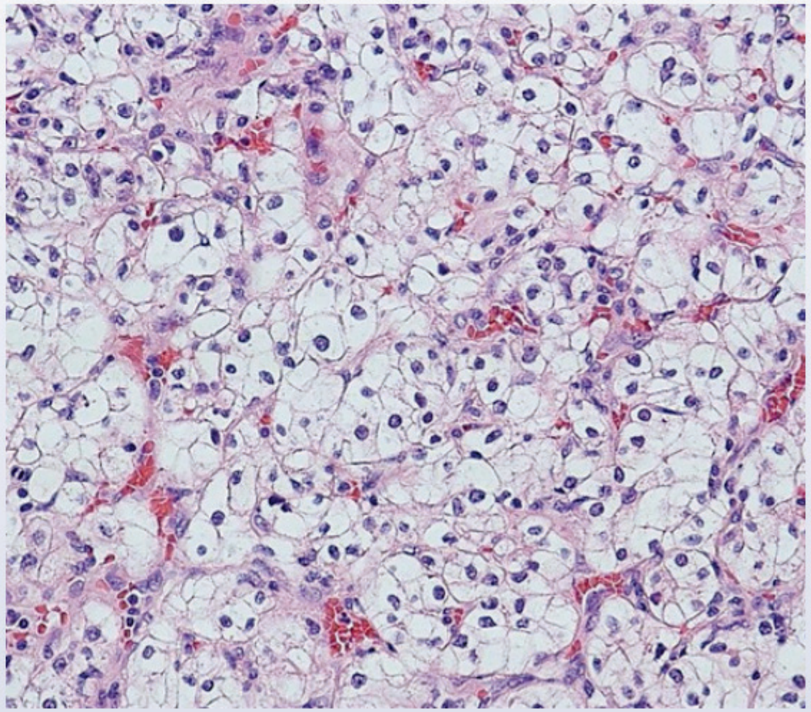
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Educational objective:
Postoperative hypocalcemia is common after thyroid surgery due to inadvertent removal or damage to the

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A 65-year-old man comes to the office for evaluation of blood in the urine. The patient has no abdominal pain, urinary frequency, or urgency. He has hypertension, type 2 diabetes mellitus, and stage II chronic kidney disease. He quit smoking 10 years ago and had smoked a pack of cigarettes daily for 30 years. On examination, vital signs are within normal limits. The patient's BMI is 33 kg/m^2. After appropriate work-up, the patient undergoes a renal biopsy; histopathologic findings are shown below.



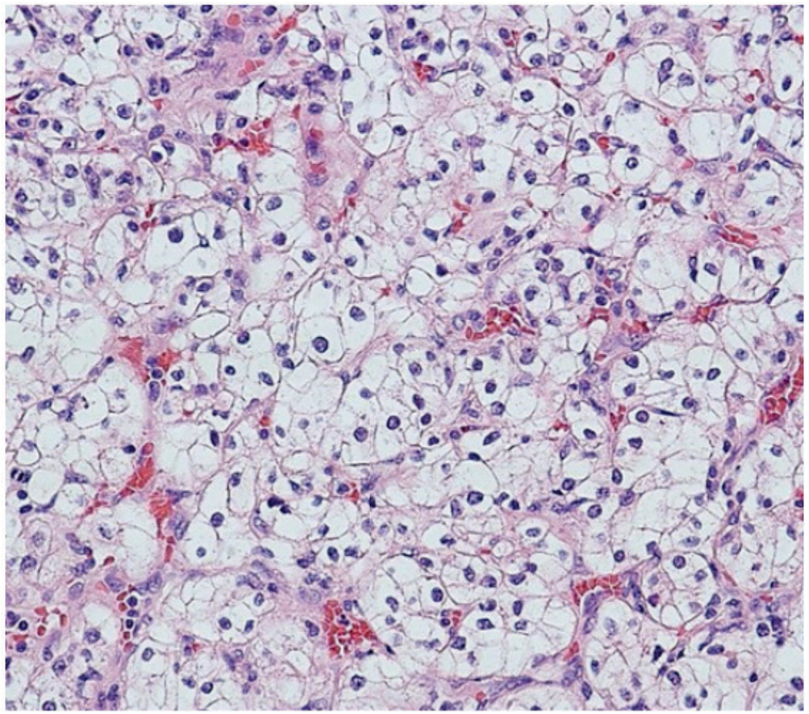
Which of the following processes most likely accounts for the abnormal appearance of these cells?

- A. Glycogen and lipid accumulation
- B. Karyorrhexis

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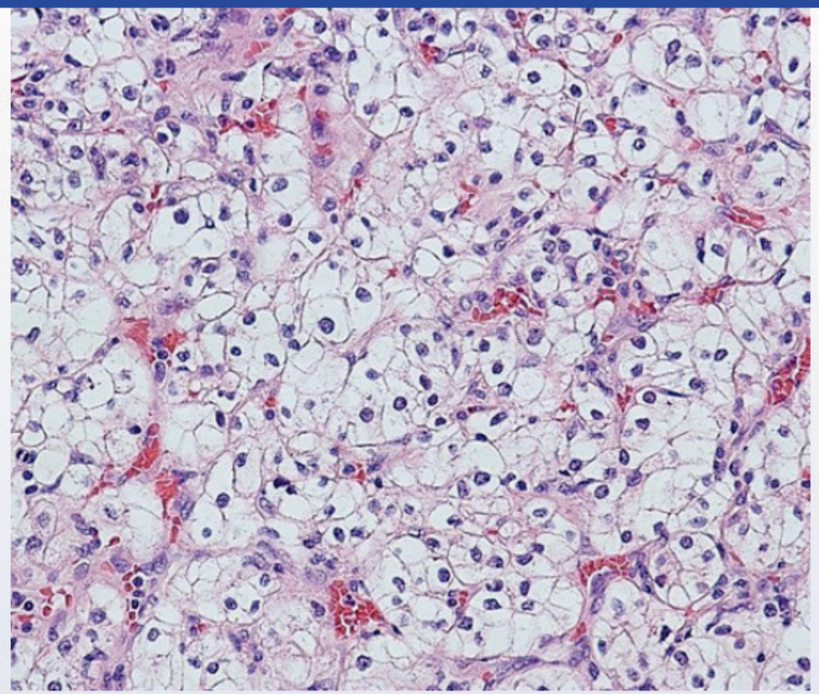


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Whi

B. Karyorrhexis

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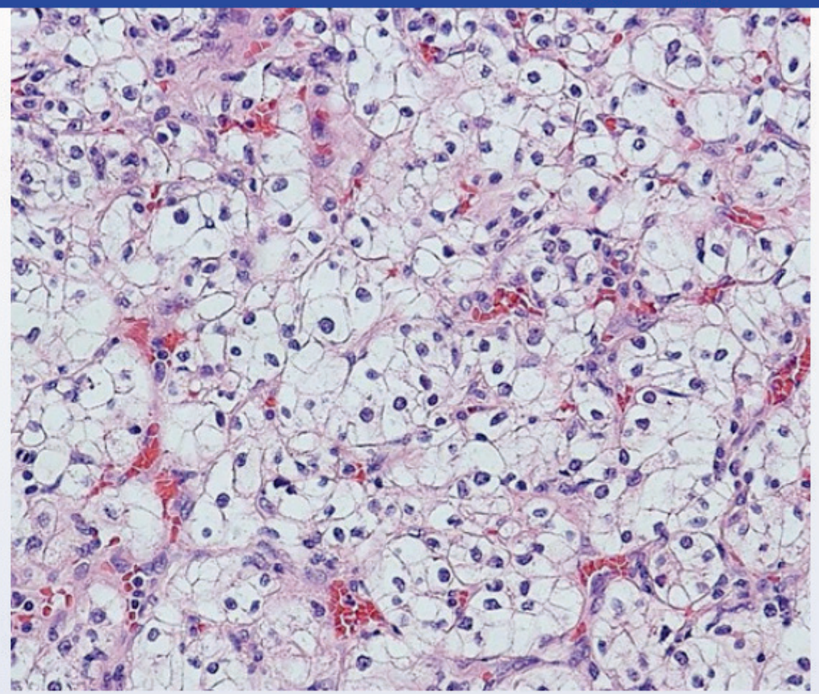


Which of the following processes most likely accounts for the abnormal appearance of these cells?

- A. Glycogen and lipid accumulation
- B. Karyorrhexis
- C. Membrane lipid peroxidation
- D. Mitochondrial swelling
- E. Pigment accumulation

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Which of the following processes most likely accounts for the abnormal appearance of these cells?

- ✓ A. Glycogen and lipid accumulation (80%)
- ✗ B. Karyorrhexis (5%)
- C. Membrane lipid peroxidation (8%)
- D. Mitochondrial swelling (4%)
- E. Pigment accumulation (1%)

Incorrect
Correct answer
A

80%
Answered correctly

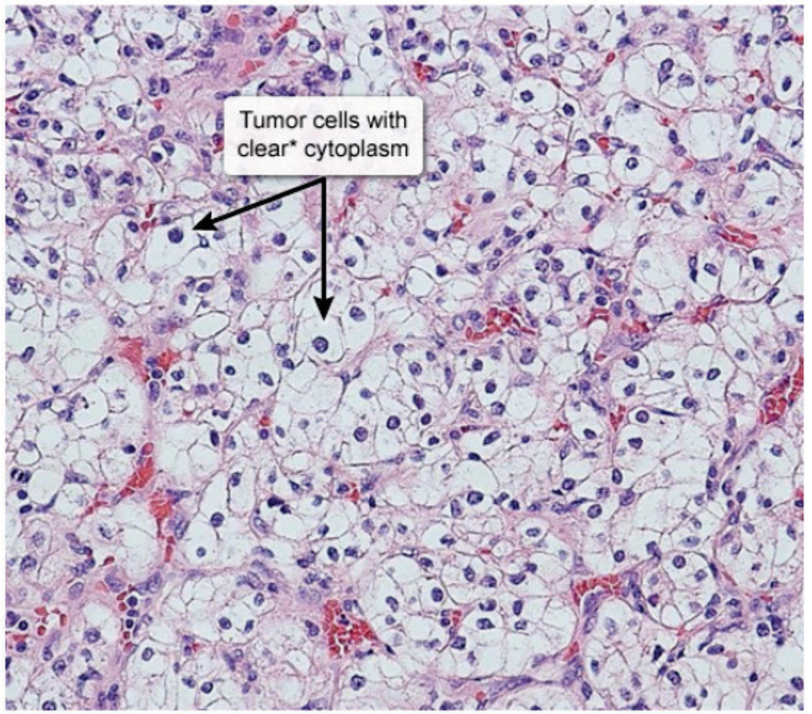
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Clear cell renal cell carcinoma



*Due to cytoplasmic glycogen and lipids

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the above image have intact nuclei.

(Choice C) Plasma membrane damage caused by lipid peroxidation can be visualized using immunofluorescent

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*Due to cytoplasmic glycogen and lipids ©UWorld

Gross painless hematuria in an older adult should be considered a sign of urinary tract cancer (urothelial or renal cell carcinoma) until proven otherwise. This patient's renal biopsy shows **rounded/polygonal cells** with abundant **clear cytoplasm**, which is characteristic of **clear cell carcinoma**, the most common form of renal cell carcinoma. Clear cell carcinoma originates from proximal tubular epithelial cells and contains copious amounts of intracellular glycogen and lipids. Standard tissue fixation and staining techniques typically dissolve glycogen and lipids from pathologic specimens, leaving **clear spaces**.

(Choice B) Karyorrhexis is fragmentation of pyknotic (condensed) nuclei during apoptotic cell death. The cells in the above image have intact nuclei.

(Choice C) Plasma membrane damage caused by lipid peroxidation can be visualized using immunofluorescent microscopy. Lipid peroxidation is a form of free radical damage and is associated with inflammation, atherosclerosis, and tumorigenesis.

(Choice D) Mitochondrial swelling usually occurs during cell injury and would not be expected to render the cell cytoplasm completely clear on routine hematoxylin and eosin stain.

(Choice E) Melanin and hemosiderin are pigments commonly seen in histologic specimens. Hemosiderin is an iron oxide pigment that stains tissues at sites of bleeding.

Educational objective:
The most common renal malignancy is clear cell carcinoma, which arises from renal proximal tubular cells. Rounded or polygonal cells with abundant clear cytoplasm are seen on light microscopy. The cells contain large amounts of glycogen and lipids that dissolve during routine tissue preparation, leaving clear spaces within the cytoplasm.

Pathology	Renal, Urinary Systems & Electrolytes	Renal cell carcinoma
Subject	System	Topic

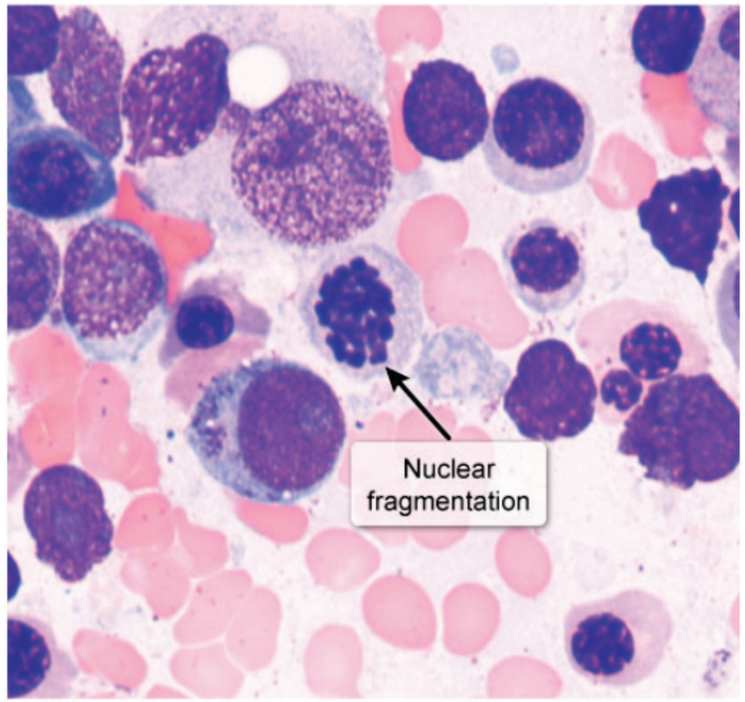
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*Due to cytoplasmic glycogen and lipids

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Karyorrhexis



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Pathology (Subject) | Renal, Urinary Systems & Electrolytes (System) | Renal cell carcinoma (Topic)

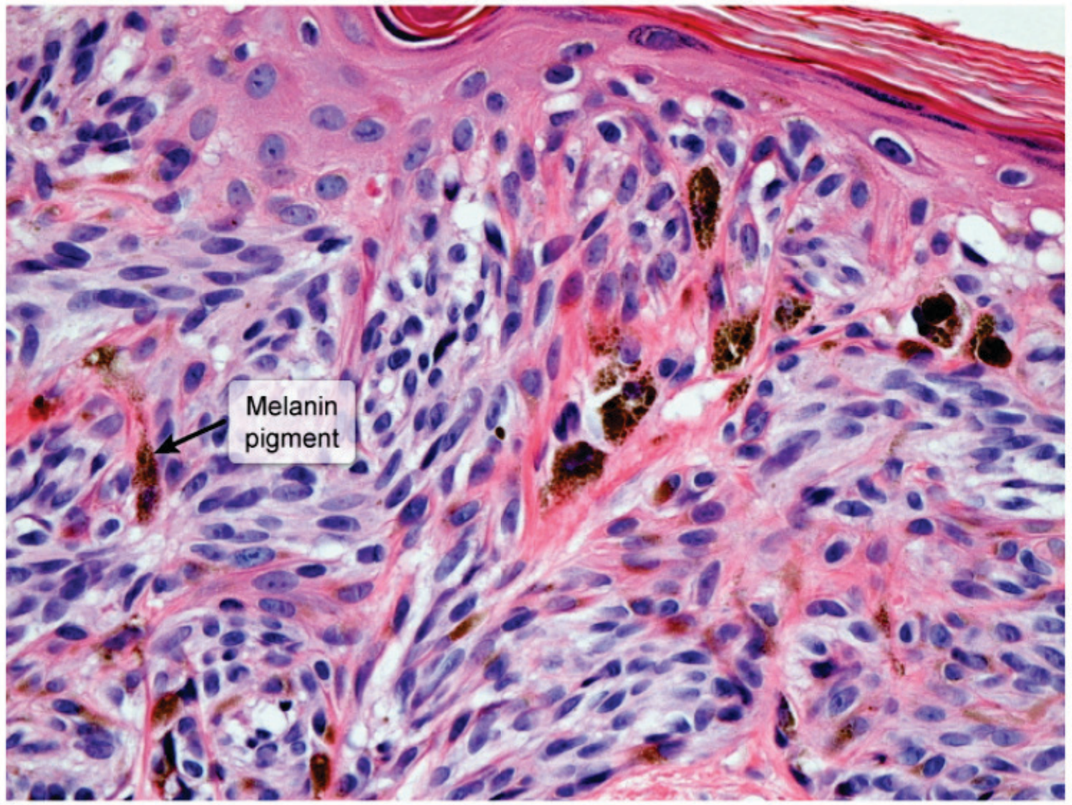
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*Due to cytoplasmic glycogen and lipids

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Melanin pigment



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Pathology (Subject) | Renal, Urinary Systems & Electrolytes (System) | Renal cell carcinoma (Topic)

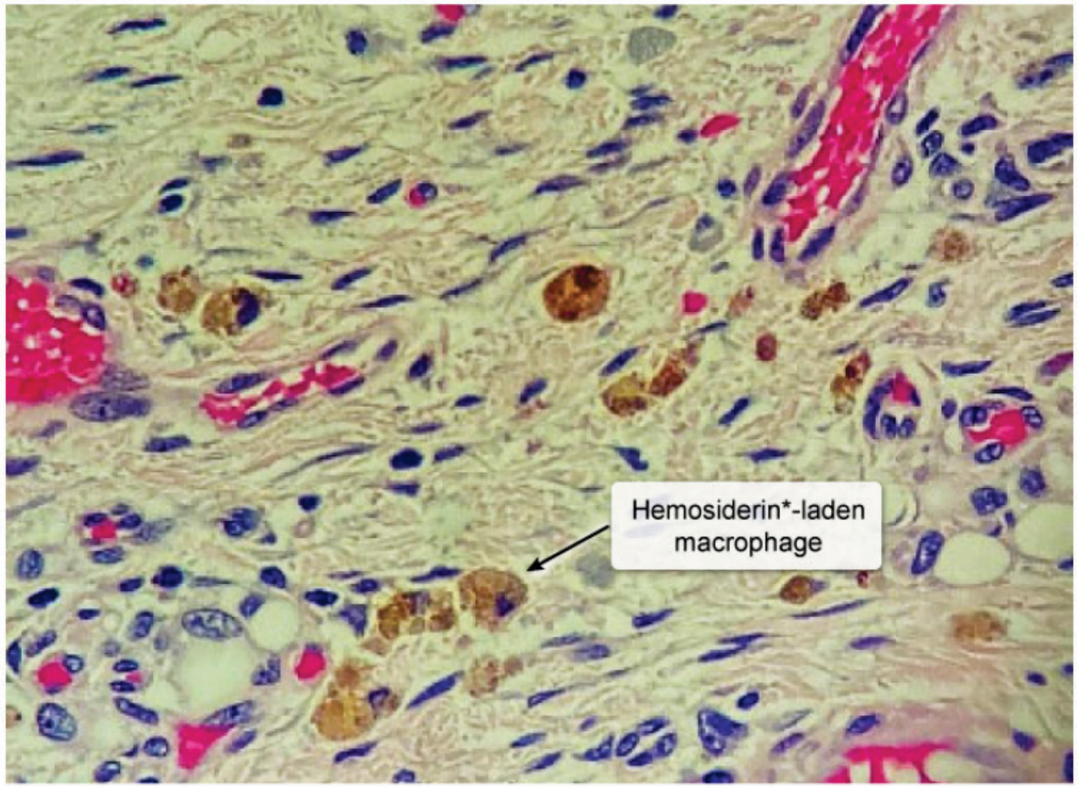
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*Due to cytoplasmic glycogen and lipids

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Hemosiderin pigment



*Iron storage form

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Pathology (Subject) | Renal, Urinary Systems & Electrolytes (System) | Renal cell carcinoma (Topic)

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A 65-year-old man comes to the office to establish medical care. The patient states that he was diagnosed with type 2 diabetes mellitus several years ago but has not taken medications or followed up. He reports no symptoms. Blood pressure is 142/86 mm Hg and pulse is 78/min. BMI is 30 kg/m^2. Physical examination shows no abnormalities. Laboratory testing shows uncontrolled diabetes mellitus with diabetic nephropathy. He also has findings indicating a decreased aldosterone effect on the renal tubules but no other adrenal or pituitary hormonal disturbances. Compared to healthy individuals, which of the following are most likely in this patient?

	Serum sodium concentration	Urinary potassium excretion	Urinary ammonium excretion
A.	Decreased	Increased	Unchanged
B.	Decreased	Unchanged	Increased
C.	Increased	Decreased	Increased
D.	Unchanged	Decreased	Decreased
E.	Unchanged	Increased	Decreased

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	Serum sodium concentration	Urinary potassium excretion	Urinary ammonium excretion	
✗ A.	Decreased	Increased	Unchanged	(21%)
B.	Decreased	Unchanged	Increased	(16%)
C.	Increased	Decreased	Increased	(12%)
✓ D.	Unchanged	Decreased	Decreased	(44%)
E.	Unchanged	Increased	Decreased	(5%)

Incorrect
Correct answer
D

44%
Answered correctly

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Explanation

This patient's decreased aldosterone effect on the kidneys is likely due to **impaired renin secretion** in the setting of juxtaglomerular apparatus destruction from **diabetic nephropathy**, with a downstream decrease in aldosterone

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Explanation

This patient's decreased aldosterone effect on the kidneys is likely due to **impaired renin secretion** in the setting of juxtaglomerular apparatus destruction from **diabetic nephropathy**, with a downstream decrease in aldosterone production. Aldosterone acts on the nephron collecting duct to stimulate sodium reabsorption, with a consequent increase in the excretion of potassium and hydrogen (H^+ is excreted in the form of ammonium [$NH4^+$]).

With decreased aldosterone activity, **potassium and H^+ excretion is decreased**, leading to hyperkalemia and metabolic acidosis. The metabolic acidosis created is nonanion gap due to the retention of H^+ and a net loss of bicarbonate (HCO_3^-). Sodium reabsorption is decreased, leading to some degree of volume depletion (total body sodium is decreased), but hyponatremia often does not occur because antidiuretic hormone levels appropriately adjust to maintain a **normal serum sodium concentration**.

A reduced aldosterone effect on the kidneys and the resulting metabolic abnormalities are referred to as **type 4 renal tubular acidosis** (RTA). In addition to diabetes mellitus, other causes of type 4 RTA include primary aldosterone deficiency and pharmacologic aldosterone inhibition such as that induced by mineralocorticoid antagonists (eg, spironolactone, eplerenone) and ENaC channel inhibitors (eg, amiloride, triamterene).

Educational objective:
Type 4 renal tubular acidosis (RTA) results from a reduced aldosterone effect on the kidneys and is characterized by hyperkalemia (reduced potassium excretion) and nonanion gap metabolic acidosis (reduced hydrogen excretion in the form of ammonium). Sodium reabsorption is decreased, leading to decreased total body sodium, but the serum sodium concentration is often unchanged due to the appropriate function of antidiuretic hormone.

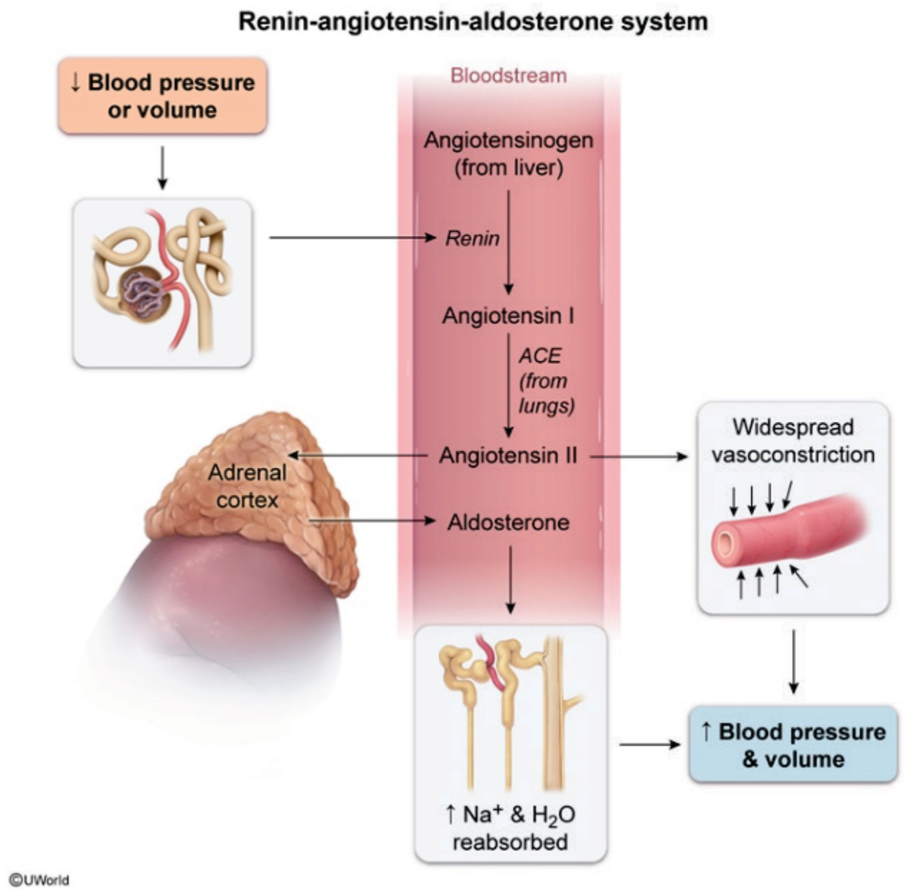
References

- Renal tubular acidosis.

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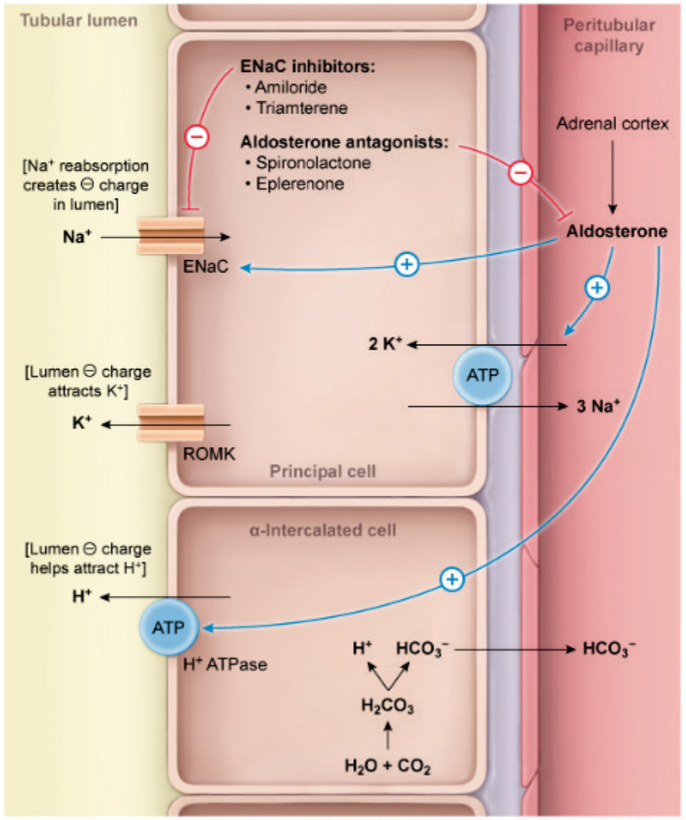
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Explanation

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Action of aldosterone in the collecting duct of the nephron



ENaC = epithelial sodium channel; **ROMK** = renal outer medullary potassium channel. ©UWorld

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Explanation

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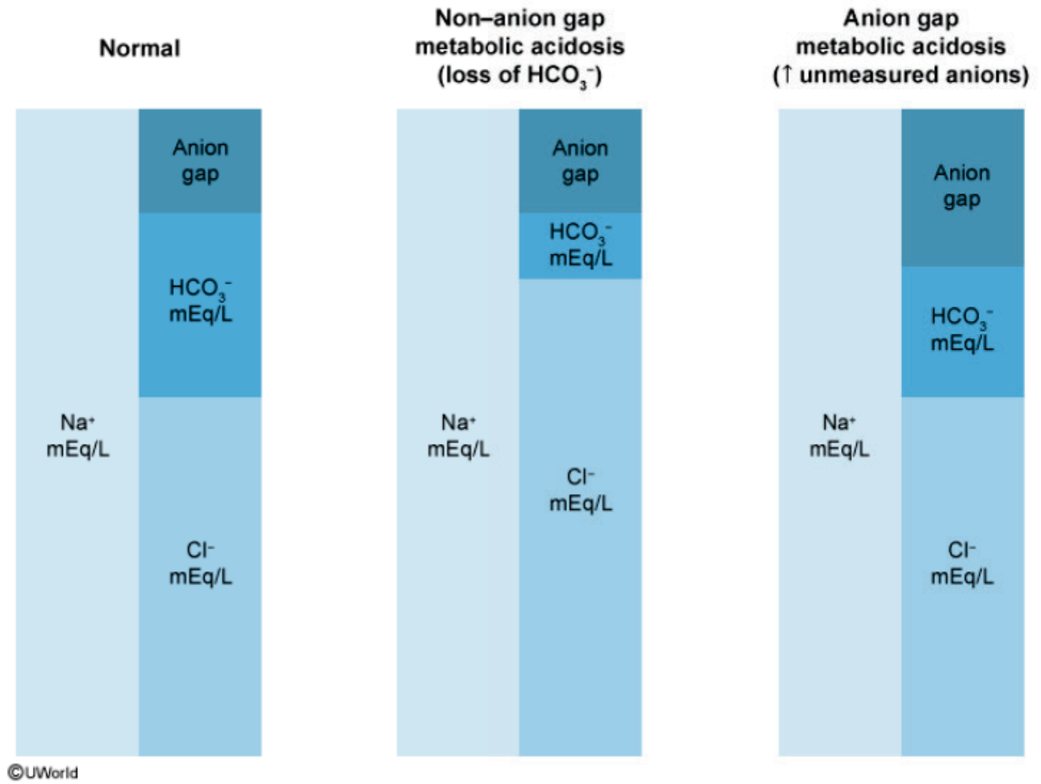
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A longitudinal study is conducted to assess changes in renal function over time in patients with recently diagnosed type 2 diabetes mellitus. An initial set of laboratory tests is obtained in newly enrolled patients to establish baseline renal function parameters. The following measurements are taken from a 42-year-old male volunteer.

	Urine	Serum
Creatinine	110.0 mg/dL	1.1 mg/dL
Glucose	0	80.0 mg/dL
Potassium	50.0 mEq/L	4.0 mEq/L
Uric acid	15.0 mg/dL	3.0 mg/dL
Para-aminohippuric acid	100 mg/mL	0.2 mg/mL

Which of the following is the best estimate of the filtration fraction in this patient assuming a urine flow of 1.0 mL/min?

- A. 10%
- B. 20%
- C. 30%
- D. 40%
- E. 50%

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type 2 diabetes mellitus. An initial set of laboratory tests is obtained in newly enrolled patients to establish baseline renal function parameters. The following measurements are taken from a 42-year-old male volunteer.

	Urine	Serum
Creatinine	110.0 mg/dL	1.1 mg/dL
Glucose	0	80.0 mg/dL
Potassium	50.0 mEq/L	4.0 mEq/L
Uric acid	15.0 mg/dL	3.0 mg/dL
Para-aminohippuric acid	100 mg/mL	0.2 mg/mL

Which of the following is the best estimate of the filtration fraction in this patient assuming a urine flow of 1.0 mL/min?

- ✗ A. 10% (18%)
- ✓ B. 20% (59%)
- C. 30% (6%)
- D. 40% (5%)
- E. 50% (10%)

Incorrect
Correct answer
B

59%
Answered correctly

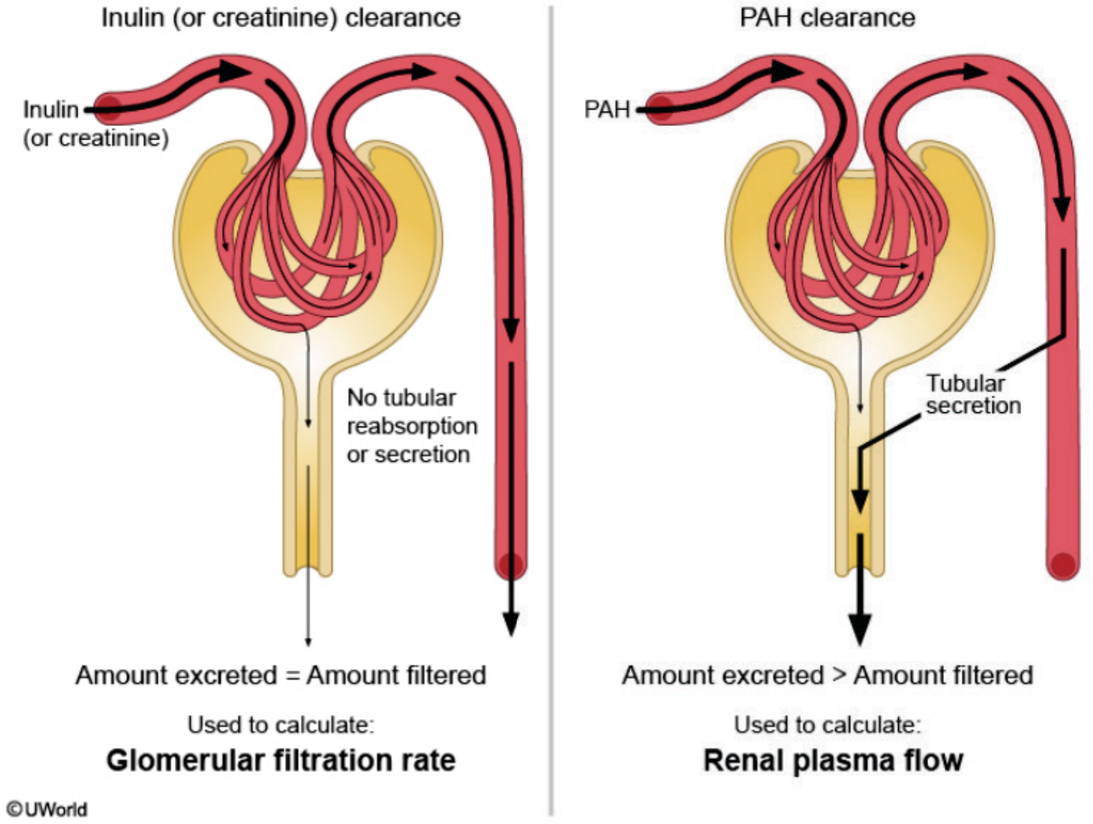
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B. 20% (59%)

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Amount excreted = Amount filtered

Amount excreted > Amount filtered

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Filtration fraction (FF) is the fraction of plasma flowing through the glomeruli that is filtered across the glomerular capillaries into Bowman's space. It can be thought of as the ratio between the glomerular filtration rate (GFR) and renal plasma flow (RPF):

FF = GFR / RPF

GFR can be calculated using the inulin or creatinine clearance, as these substances are freely filtered at the glomerulus and have relatively insignificant tubular reabsorption or secretion. RPF can be determined using the para-aminohippuric acid (PAH) clearance as almost all the PAH entering the kidneys is excreted in the urine (mostly via tubular secretion).

The clearance (C) of any given substance S can be calculated as:

C_s = ([Urine concentration of S] x [Urine flow rate]) / (Plasma concentration of S)

In this example, creatinine and PAH clearances can be calculated as:

$C_{Creatinine}$ = (110 mg/dl x 1 ml/min) / 1.1 mg/dl = 100 ml/min

C_{PAH} = (100 mg/ml x 1 ml/min) / 0.2 mg/ml = 500 ml/min

From these values, FF can then be calculated as (100 ml/min) / (500 ml/min) = 0.2 or 20%, which is the typical filtration fraction for a healthy individual.

Educational objective:
The glomerular filtration rate (GFR) can be estimated by the inulin or creatinine clearance, while the renal plasma flow (RPF) is calculated using the para-aminohippuric acid clearance. The filtration fraction (FF = GFR / RPF) is the fraction of the RPF that is filtered across the glomerular capillaries into Bowman's space. It is usually equal to 20% in healthy individuals.

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A 24-year-old woman with a medical history of bronchial asthma comes to the office due to shortness of breath and wheezing for the past 2-3 days. She developed a cold 4 days ago and is not feeling well. The patient has a nebulizer at home and used multiple doses of albuterol with little response prior to arriving. She takes no other medications. The patient is diaphoretic and in moderate respiratory distress. Respiratory examination shows bilateral wheezing, diffusely decreased breath sounds, and increased use of accessory muscles of respiration. Laboratory results reveal a serum potassium of 3 mEq/L. Which of the following mechanisms is the most likely cause of this patient's hypokalemia?

- A. Decreased oral intake of potassium
- B. Development of respiratory acidosis
- C. Increased sweat loss of potassium
- D. Increased urinary excretion of potassium
- E. Intracellular shift of potassium

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A 24-year-old woman with a medical history of bronchial asthma comes to the office due to shortness of breath and wheezing for the past 2-3 days. She developed a cold 4 days ago and is not feeling well. The patient has a nebulizer at home and used multiple doses of albuterol with little response prior to arriving. She takes no other medications. The patient is diaphoretic and in moderate respiratory distress. Respiratory examination shows bilateral wheezing, diffusely decreased breath sounds, and increased use of accessory muscles of respiration. Laboratory results reveal a serum potassium of 3 mEq/L. Which of the following mechanisms is the most likely cause of this patient's hypokalemia?

- A. Decreased oral intake of potassium (0%)
- ✗ B. Development of respiratory acidosis (14%)
- C. Increased sweat loss of potassium (1%)
- D. Increased urinary excretion of potassium (12%)
- ✓ E. Intracellular shift of potassium (71%)

Incorrect
Correct answer
E

71%
Answered correctly

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Explanation

Causes of hypokalemia	
Decreased intake	• Starvation, anorexia
	• Insulin (eg, treatment of DKA, refeeding syndrome)

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Causes of hypokalemia	
Decreased intake	• Starvation, anorexia
Intracellular translocation	• Insulin (eg, treatment of DKA, refeeding syndrome) • β-adrenergic activity ◦ Pharmacologic (eg, albuterol, dobutamine) ◦ Stress-induced (eg, alcohol withdrawal, acute MI) • Alkalosis (respiratory or metabolic) • ↑ Cell reproduction (eg, acute myeloid leukemia, GM-CSF)
Gastrointestinal loss	• Diarrhea, vomiting, hyperaldosteronism
Urinary loss	• Hyperaldosteronism, diuretics, RTA types 1 and 2
Sweat loss	• Extreme exercise in hot climate

DKA = diabetic ketoacidosis; **MI** = myocardial infarction; **GM-CSF** = granulocyte-macrophage colony-stimulating factor; **RTA** = renal tubular acidosis.

Hypokalemia is a common medical condition that can result from several mechanisms, including decreased oral intake, renal or gastrointestinal loss, and increased entry into cells. In a patient receiving multiple doses of albuterol, the most likely etiology is **intracellular shift of potassium**.

Potassium is primarily stored intracellularly (~98% of total body stores) through the action of the **Na-K-ATPase pump**, which exchanges sodium for potassium against their concentration gradient. The large concentration difference of intracellular (~150 mEq/L) to extracellular potassium (~4 mEq/L) is a major driver of the resting membrane potential. Alterations in this ratio can impair action potential generation, explaining why patients with marked hyper- or hypokalemia can develop muscular weakness and cardiac arrhythmias.

Beta-adrenergic activity increases the activity of the Na-K-ATPase pump; therefore, both endogenous

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Hypokalemia is a common medical condition that can result from several mechanisms, including decreased oral intake, renal or gastrointestinal loss, and increased entry into cells. In a patient receiving multiple doses of albuterol, the most likely etiology is **intracellular shift of potassium**.

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Beta-adrenergic activity increases the activity of the Na-K-ATPase pump; therefore, both endogenous catecholamines and therapeutic beta-2 agonists (eg, **albuterol**, dobutamine) can cause **transient hypokalemia** due to increased **transport of potassium intracellularly**. Similar effects can also occur with sympathomimetics (eg, pseudoephedrine) and insulin, which also increase Na-K-ATPase activity.

(Choice A) Decreased oral intake of potassium is a rare cause of hypokalemia. Because the kidneys can lower potassium excretion in the setting of reduced potassium intake, most patients do not develop hypokalemia unless fasting is prolonged (eg, starvation).

(Choice B) Respiratory acidosis may occur as a complication of asthma or chronic obstructive pulmonary disease due to CO_2 retention; however, acidosis causes potassium to shift to the extracellular space, leading to hyperkalemia (not hypokalemia). In contrast, alkalosis causes intracellular shift of potassium, resulting in transient hypokalemia.

(Choice C) Significant diaphoresis (eg, marathon running in a hot climate) can result in potassium depletion. However, normal sweating (as could occur in patients with increased work of breathing) would not result in significant potassium loss.

(Choice D) Increased urinary potassium loss can occur due to diuretic use or elevated aldosterone levels (eg, renovascular disease, primary hyperaldosteronism). While beta-1 agonists can result in increased renin release

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Beta-adrenergic activity increases the activity of the Na-K-ATPase pump; therefore, both endogenous catecholamines and therapeutic beta-2 agonists (eg, **albuterol**, dobutamine) can cause **transient hypokalemia** due to increased **transport of potassium intracellularly**. Similar effects can also occur with sympathomimetics (eg, pseudoephedrine) and insulin, which also increase Na-K-ATPase activity.

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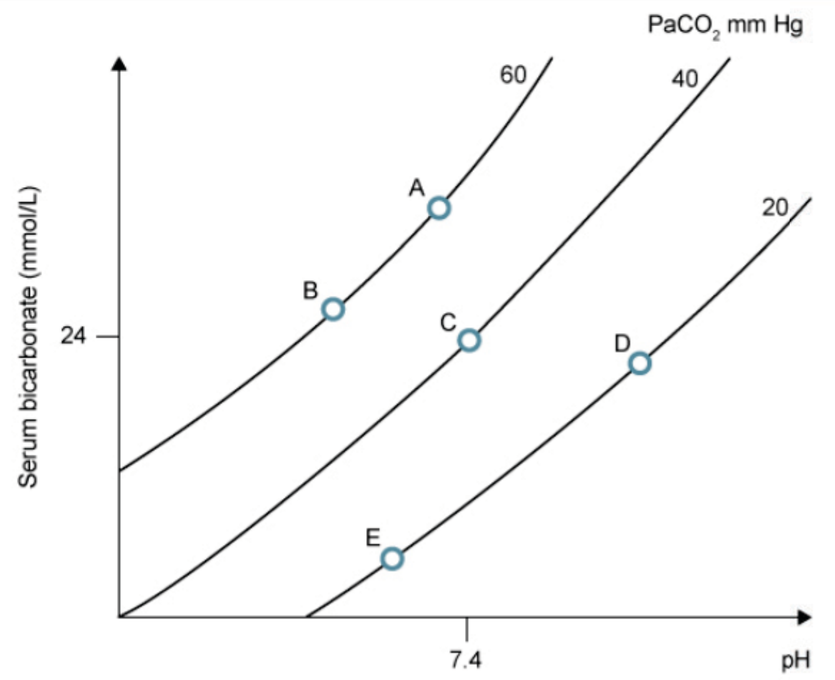
(Choice D) Increased urinary potassium loss can occur due to diuretic use or elevated aldosterone levels (eg, renovascular disease, primary hyperaldosteronism). While beta-1 agonists can result in increased renin release (leading to elevated aldosterone levels and increased renal potassium loss), beta-2 agonists (eg, albuterol) do not have a significant effect on urinary potassium excretion.

Educational objective:
Potassium is primarily stored intracellularly (~98% of total body stores) through the action of the Na-K-ATPase pump. Beta-adrenergic activity increases the activity of the Na-K-ATPase pump; therefore, both endogenous catecholamines and therapeutic beta-2 agonists (eg, albuterol, dobutamine) can cause transient hypokalemia due to increased transport of potassium intracellularly.

Pharmacology Renal, Urinary Systems & Electrolytes Beta 2 agonists

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A 23-year-old man comes to the emergency department due to abdominal pain and nausea for the last few hours. He also reports an episode of vomiting and has noticed that his urine has a fruity odor. The patient has had increased thirst and urination for the past several days along with weight loss. He has no known medical problems and takes no medications. Physical examination reveals pallor with cool extremities. The abdomen is soft, without tenderness to palpation. Laboratory studies are ordered to confirm the diagnosis. Which of the following points on the graph below best corresponds to this patient's acid-base status?

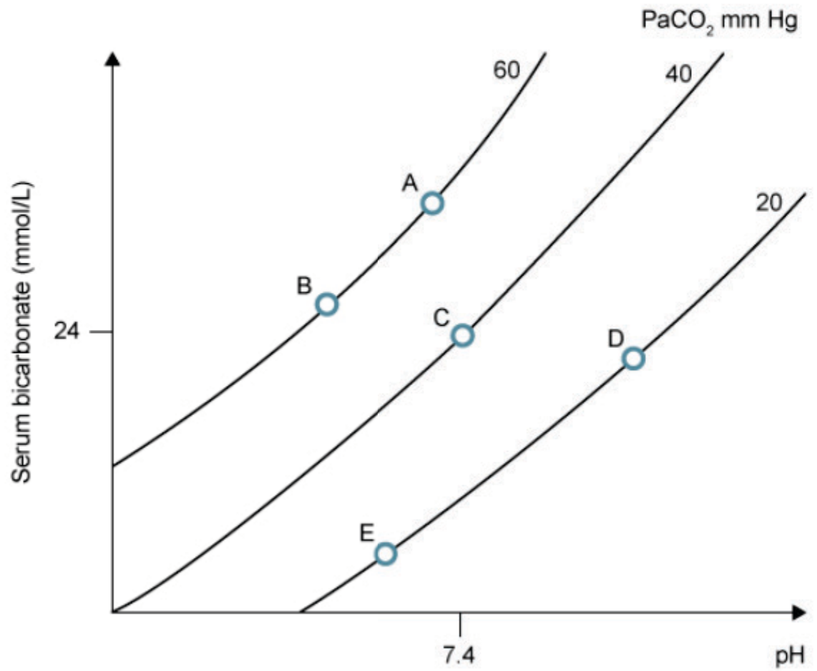


- A. Point A
- B. Point B
- C. Point C

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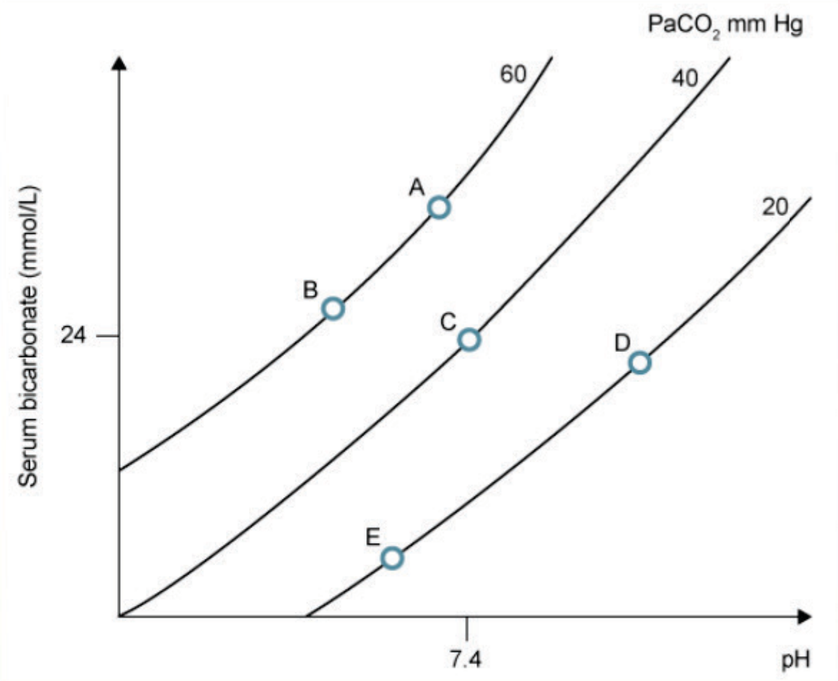


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C. Point C

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the graph below best corresponds to this patient's acid-base status?

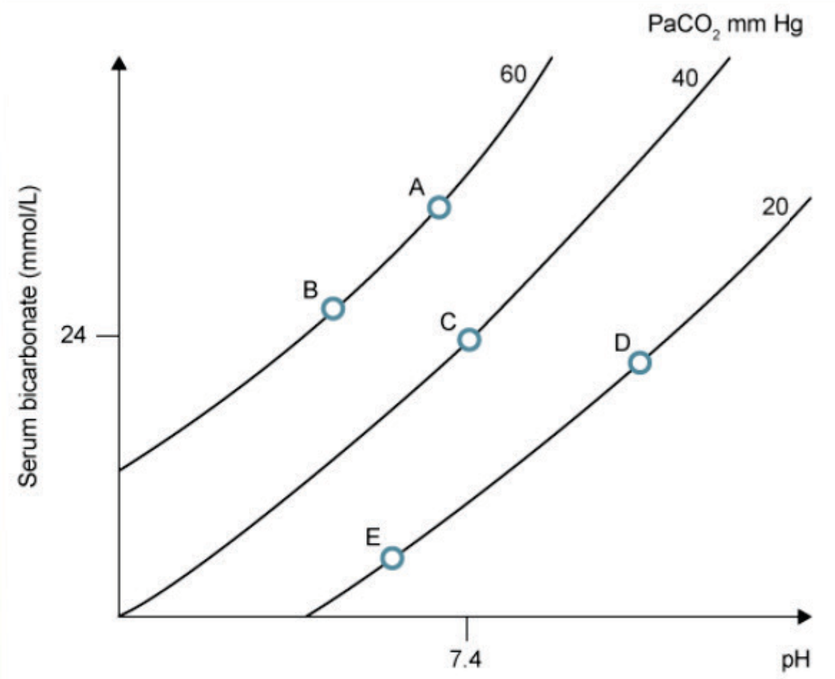


- A. Point A
- B. Point B
- C. Point C
- D. Point D
- E. Point E

Submit

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the graph below best corresponds to this patient's acid-base status?



- A. Point A (3%)
- ✗ B. Point B (12%)
- C. Point C (3%)
- D. Point D (5%)
- ✓ E. Point E (75%)

Incorrect
Correct answer
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75%
Answered correctly

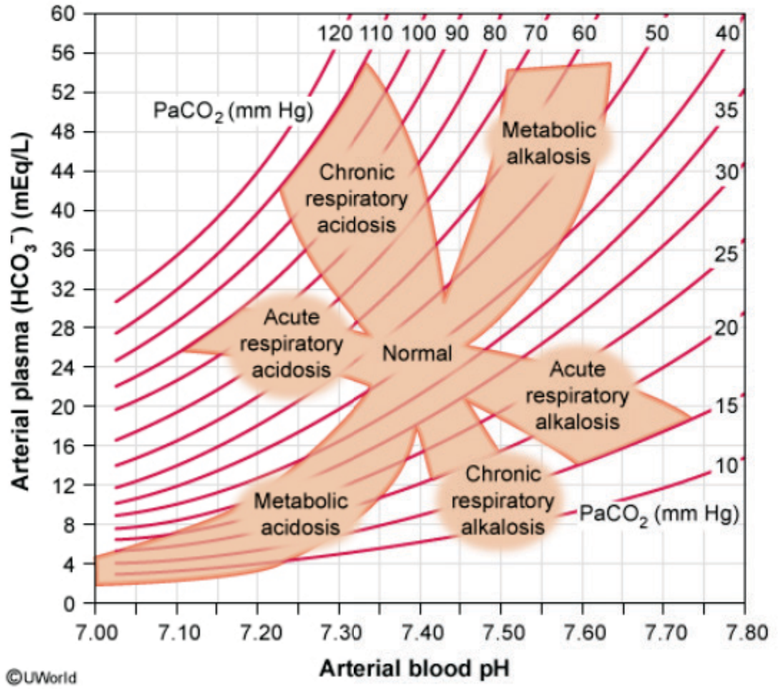
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E Point E (75%)

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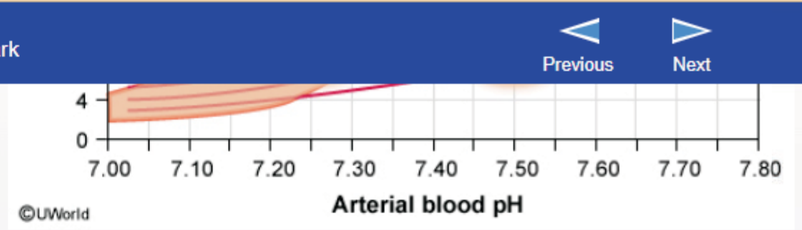


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Diab

Patients frequently present with abdominal pain, nausea, and vomiting (as seen in this patient). Laboratory results reveal **elevated anion gap metabolic acidosis** secondary to accumulation of **ketone bodies** (eg, beta

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Diabetic ketoacidosis (DKA) is characterized by polydipsia, polyuria, and a fruity odor to the breath and/or urine. Patients frequently present with abdominal pain, nausea, and vomiting (as seen in this patient). Laboratory results reveal **elevated anion gap metabolic acidosis** secondary to accumulation of **ketone bodies** (eg, beta-hydroxybutyrate and acetoacetate); excreted acetone causes the fruity smell associated with DKA. Serum bicarbonate is used to buffer the excess ketoacids in the blood, so the **bicarbonate level falls**. Metabolic acidosis also stimulates ventilation by a chemoreceptor reflex that causes **compensatory respiratory alkalosis**, which lowers CO_2 partial pressure.

The normal acid-base balance in a healthy individual is represented in the graph above by Point C **(Choice C)**. An individual with DKA will have low blood pH, low serum HCO_3^-, and low $PaCO_2$ (Point E).

(Choices A and B) Point B corresponds to a primary respiratory acidosis (low pH and high $PaCO_2$). Point A reflects chronic respiratory acidosis with compensatory metabolic alkalosis (renal retention of bicarbonate).

(Choice D) Point D corresponds to a primary respiratory alkalosis as seen in hyperventilatory states (eg, pulmonary embolism, anxiety, high altitude).

Educational objective:
Diabetic ketoacidosis (DKA) is characterized by polydipsia, polyuria, and a fruity odor to the breath and/or urine. DKA is associated with elevated anion gap metabolic acidosis that is usually accompanied by compensatory respiratory alkalosis. This combination yields a low pH, low serum bicarbonate, and low $PaCO_2$.

Physiology	Renal, Urinary Systems & Electrolytes	Diabetic ketoacidosis
Subject	System	Topic

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A 30-year-old previously healthy man is evaluated for fatigue, muscle weakness, and occasional headaches over the past several months. Blood pressure is 180/110 mm Hg, and pulse is 80/min. Laboratory evaluation reveals low serum potassium and markedly depressed plasma renin activity. CT scan of the abdomen demonstrates a right-sided adrenal mass. Treatment options are discussed, and pharmacologic therapy is begun. On a follow-up visit after several weeks of treatment, the patient reports improvement of his symptoms. Blood pressure is 130/70 mm Hg, and pulse is 75/min. Which of the following medications was most likely prescribed to this patient?

- A. Amlodipine
- B. Captopril
- C. Clonidine
- D. Hydrochlorothiazide
- E. Isosorbide dinitrate
- F. Propranolol
- G. Spironolactone
- H. Verapamil

Submit

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- A. Amlodipine (2%)
- ✗ B. Captopril (7%)
- C. Clonidine (3%)
- D. Hydrochlorothiazide (3%)
- E. Isosorbide dinitrate (1%)
- F. Propranolol (6%)
- ✓ G. Spironolactone (74%)
- H. Verapamil (0%)

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Correct answer
G

74%
Answered correctly

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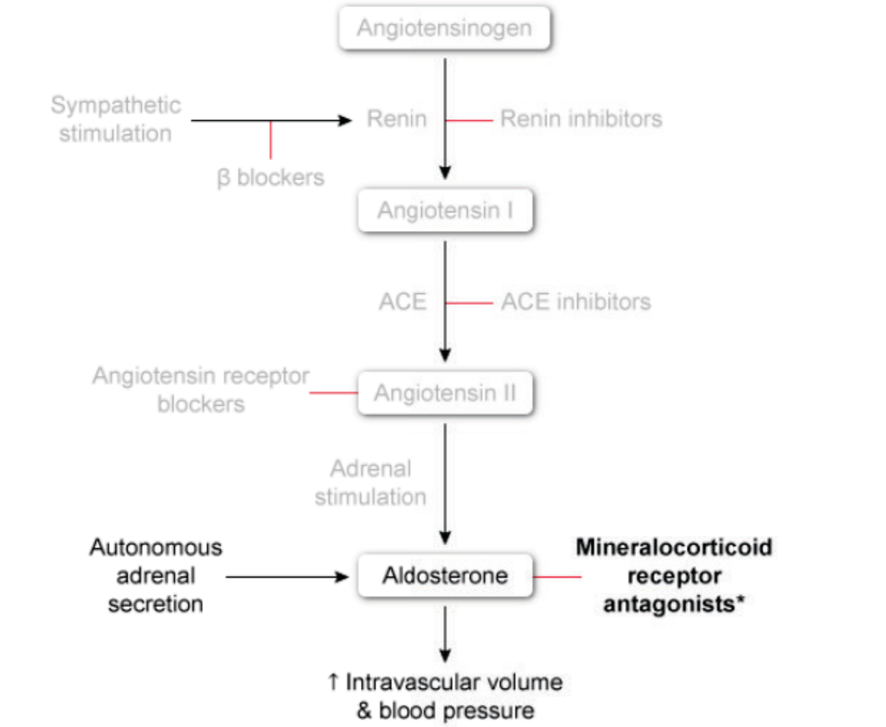
Pharmacologic management of primary hyperaldosteronism

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Pharmacologic management of primary hyperaldosteronism



*Mineralocorticoid receptor antagonists (eg, spironolactone) are the only renin-angiotensin-aldosterone system inhibitors that address autonomous aldosterone secretion.

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This patient's new-onset hypertension, symptomatic hypokalemia (eg, fatigue, muscle weakness), and **low plasma**

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aldosterone system inhibitors that address autonomous aldosterone secretion. ©UWorld

This patient's new-onset hypertension, symptomatic hypokalemia (eg, fatigue, muscle weakness), and **low plasma renin** activity are indicative of **primary hyperaldosteronism**. Primary hyperaldosteronism involves unregulated aldosterone secretion, typically due to either an adrenal adenoma—as suggested by this patient's CT finding of a unilateral **adrenal mass**—or bilateral adrenal hyperplasia.

Aldosterone, which is a mineralocorticoid normally regulated by angiotensin II and potassium (K^+) levels, stimulates reabsorption of sodium (Na^+) and secretion of K^+ and hydrogen (H^+) in the renal collecting ducts. Excess aldosterone therefore causes intravascular volume retention and **hypertension** (which can cause headache if severe), in addition to predisposing to **hypokalemia** and metabolic alkalosis. Depressed plasma renin activity also occurs due to **feedback suppression** of the renin-angiotensin-aldosterone system.

An adrenal adenoma is typically treated with adrenalectomy; however, patients who are not surgical candidates or those who decline surgery can be treated with a mineralocorticoid receptor antagonist (MRA). MRAs block the effects of excess aldosterone, thereby reducing blood pressure and treating hypokalemia and metabolic alkalosis. **Spironolactone** is most commonly used; eplerenone is less likely to cause adverse endocrine effects (eg, gynecomastia, decreased libido).

(Choices A, B, C, D, E, F, and H) Other antihypertensive medications are unlikely to normalize blood pressure in patients with primary hyperaldosteronism because these medications do not address the excess levels of aldosterone. Inhibitors of the renin-angiotensin-aldosterone system other than MRAs (eg, ACE inhibitors, beta blockers) have little effect on aldosterone levels in these patients because aldosterone release is *autonomous and independent* of angiotensin II stimulation.

Educational objective:
Primary hyperaldosteronism involves excess aldosterone secretion, which causes hypertension and predisposes to hypokalemia and metabolic alkalosis; low plasma renin activity helps distinguish it from other causes of excess aldosterone (eg, renovascular disease). First-line medical therapy for primary hyperaldosteronism includes mineralocorticoid receptor antagonist (eg, spironolactone, eplerenone).

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Educational objective:
Primary hyperaldosteronism involves excess aldosterone secretion, which causes hypertension and predisposes to hypokalemia and metabolic alkalosis; low plasma renin activity helps distinguish it from other causes of excess aldosterone (eg, renovascular disease). First-line medical therapy for primary hyperaldosteronism includes mineralocorticoid receptor antagonist (eg, spironolactone, eplerenone).

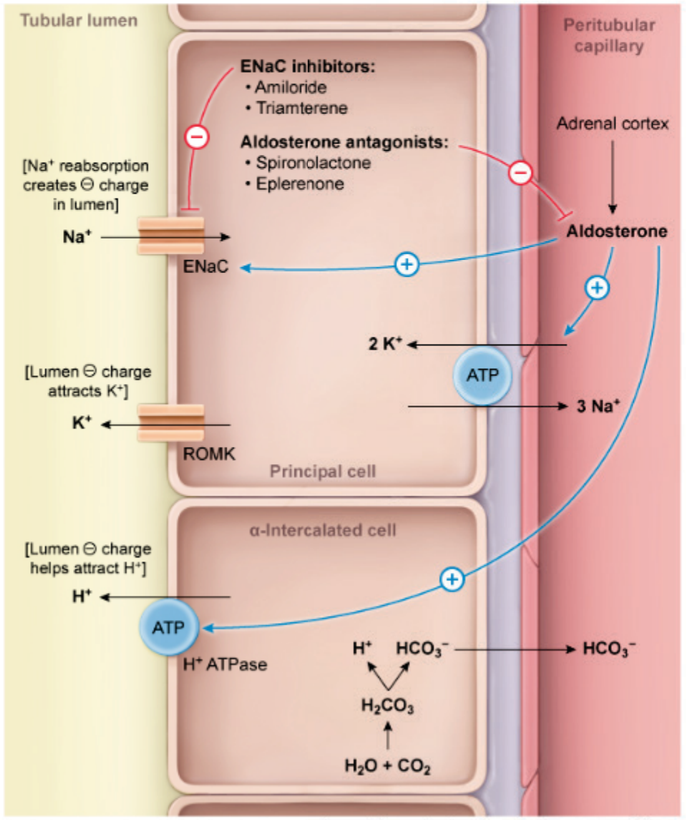
Pharmacology	Renal, Urinary Systems & Electrolytes	Hyperaldosteronism
Subject	System	Topic

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↑ Intravascular volume

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Action of aldosterone in the collecting duct of the nephron



ENaC = epithelial sodium channel; **ROMK** = renal outer medullary potassium channel. ©UWorld

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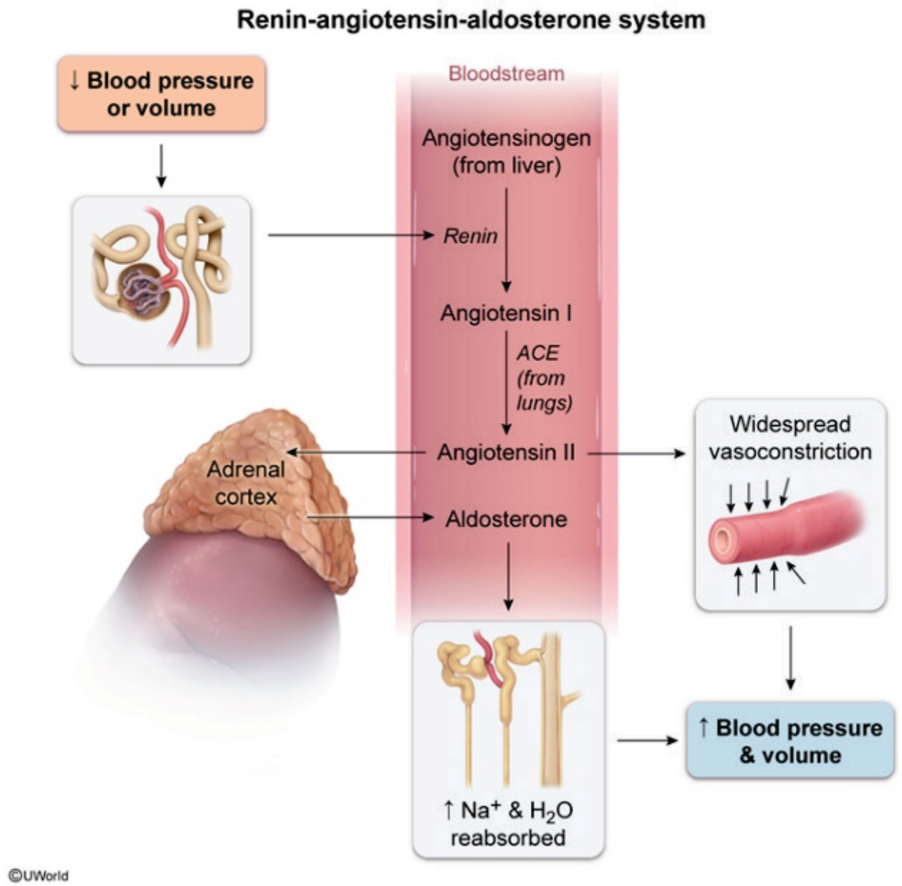
Educational objective:

Primary hyperaldosteronism involves excess aldosterone secretion, which causes hypertension and predisposes to

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↑ Intravascular volume

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Educational objective:

Primary hyperaldosteronism involves excess aldosterone secretion, which causes hypertension and predisposes to

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Scientists studying the kidney's response to hypoperfusion apply a clip to a pig's right renal artery that reduces blood flow to the kidney by about 70%. After 6 months, they perform a right nephrectomy and examine the glomeruli and tubules microscopically. Which of the following cell types would be most likely to undergo hyperplasia as a result of the clip placement?

- A. Cuboidal epithelial cells of the proximal tubules
- B. Endothelial cells of the efferent arteriole
- C. Intraglomerular mesangial cells
- D. Modified smooth muscle cells of the afferent arteriole
- E. Squamous epithelial cells of the thick ascending limb of the loop of Henle

Submit

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- A. Cuboidal epithelial cells of the proximal tubules (10%)
- B. Endothelial cells of the efferent arteriole (22%)
- ✗ C. Intraglomerular mesangial cells (20%)
- ✓ D. Modified smooth muscle cells of the afferent arteriole (43%)
- E. Squamous epithelial cells of the thick ascending limb of the loop of Henle (2%)

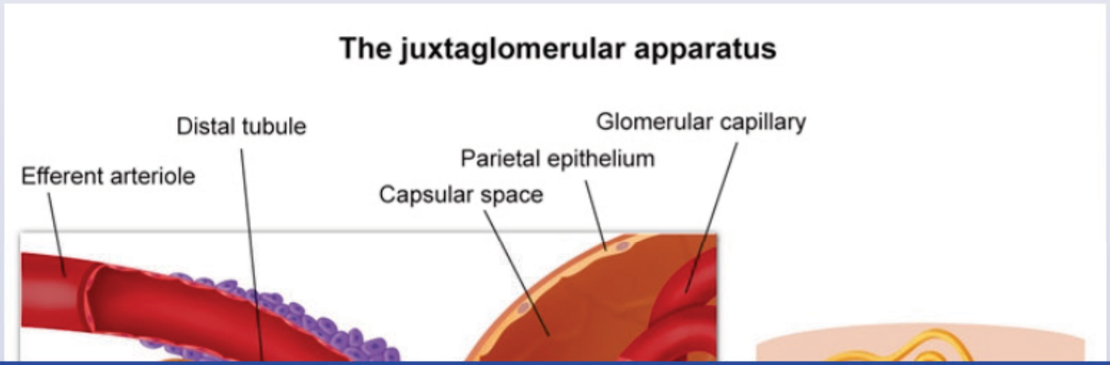
Incorrect
Correct answer
D

43%
Answered correctly

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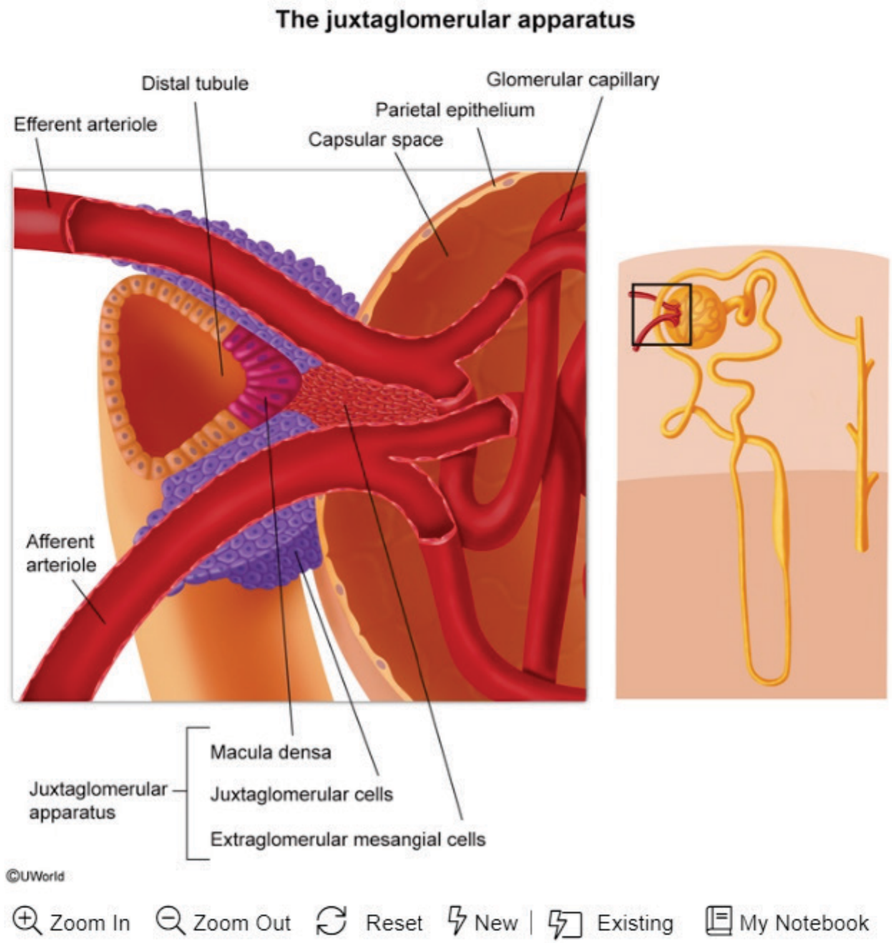
Explanation



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Scientists studying the kidney's response to hypoperfusion apply a clip to a pig's right renal artery that reduces
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A markedly narrowed renal artery (eg, due to an atherosclerotic plaque or external clip) cannot supply the kidney with enough blood to maintain a normal glomerular filtration rate. The reduced blood flow is sensed by the juxtaglomerular (JG) apparatus, which consists of the macula densa, extraglomerular mesangial cells (ie, Lacis cells), and JG cells. **Macula densa** cells are tall, narrow cells located in the **distal tubule** that monitor salt content and tubular flow rate. This information is transmitted to nearby **JG cells** that are located mainly in the wall of the **afferent arteriole**. JG cells are **modified smooth muscle cells** with renin-containing zymogen granules.

Significant **renal hypoperfusion** leads to a compensatory **increase in renin secretion** by JG cells. This activates the renin-angiotensin-aldosterone system, leading to increased levels of angiotensin II and aldosterone. Long-term renal hypoperfusion, such as caused by renal artery stenosis, leads the JG cells of the affected kidney(s) to undergo **hyperplasia** as a result of chronic stimulation.

When renal artery stenosis is restricted to one side and the contralateral kidney functions normally, chronic kidney disease does not occur as the normal kidney is still able to efficiently filter and excrete waste products (eg, creatinine, urea). However, hypertension can occur in both unilateral and bilateral disease, as secretion of renin by one kidney will lead to systemic vasoconstriction and retention of salt and water by both kidneys.

(Choices A, C, and E) The cuboidal cells of the proximal tubule, the intraglomerular mesangial cells (which are distinct from the extraglomerular mesangial [Lacis] cells), and the squamous cells of the thick ascending limb of the loop of Henle are not components of the JG apparatus and do not undergo hyperplasia in response to hypoperfusion. In fact, these tissues may atrophy in the clipped kidney due to ischemia.

(Choice B) The endothelium is composed of a single layer of squamous cells that line blood vessel walls; endothelial cells do not undergo hyperplasia in response to hypoperfusion. Efferent arteriolar smooth muscle cells may undergo hypertrophy/hyperplasia with chronic angiotensin stimulation, but these lie within the arteriolar wall (underneath the endothelium).

Educational objective:
Renal artery stenosis causing significant renal hypoperfusion will result in a decreased glomerular filtration rate and

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cells), and JG cells. **Macula densa** cells are tall, narrow cells located in the **distal tubule** that monitor salt content and tubular flow rate. This information is transmitted to nearby **JG cells** that are located mainly in the wall of the **afferent arteriole**. JG cells are **modified smooth muscle cells** with renin-containing zymogen granules.

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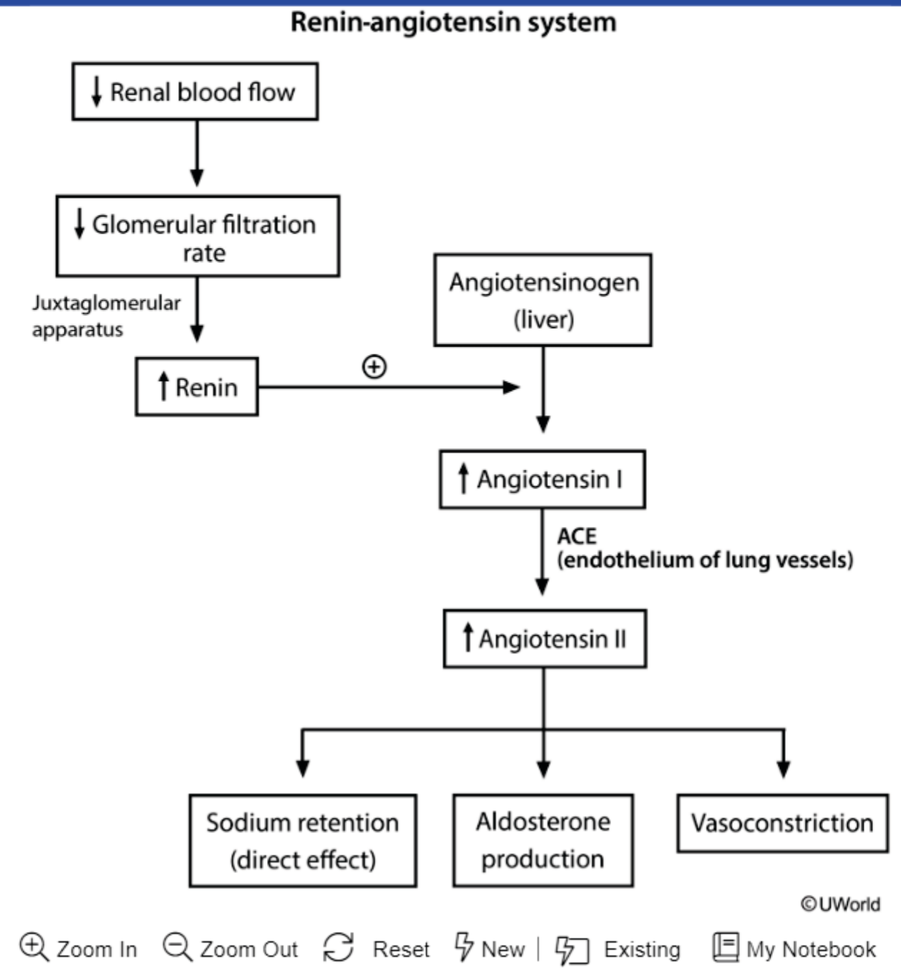
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Educational objective:
Renal artery stenosis causing significant renal hypoperfusion will result in a decreased glomerular filtration rate and activation of the renin-angiotensin-aldosterone system. This leads to increased renin release by modified smooth muscle (juxtaglomerular) cells in the walls of afferent glomerular arterioles. Chronic renal hypoperfusion can cause hyperplasia of the juxtaglomerular apparatus.

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Juxtaglomerular apparatus | Juxtaglomerular cells

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may undergo hypertrophy/hyperplasia with chronic angiotensin stimulation, but these lie within the arteriolar wall

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A 45-year-old woman comes to the office due to polyuria and nocturia. She has no fever, dysuria, or abdominal pain. The patient has no significant medical problems and takes no medications. Her temperature is 36.7 C (98 F), blood pressure is 120/80 mm Hg, and pulse is 76/min. The patient's mucous membranes appear dry. The remainder of her physical examination is normal. Her urine output and osmolality remain unchanged with water deprivation for several hours, but after administration of desmopressin, urine output decreases and urine osmolality increases. Renal clearance of which of the following substances would decrease the most after this patient's injection?

- A. Calcium
- B. Creatinine
- C. Glucose
- D. Para-amino hippuric acid
- E. Urea

Submit

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- A. Calcium (13%)
- ✗ B. Creatinine (9%)
- C. Glucose (10%)
- D. Para-amino hippuric acid (13%)
- ✓ E. Urea (53%)

Incorrect
Correct answer
E

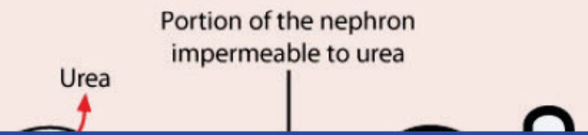
53%
Answered correctly

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Time Spent

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Explanation

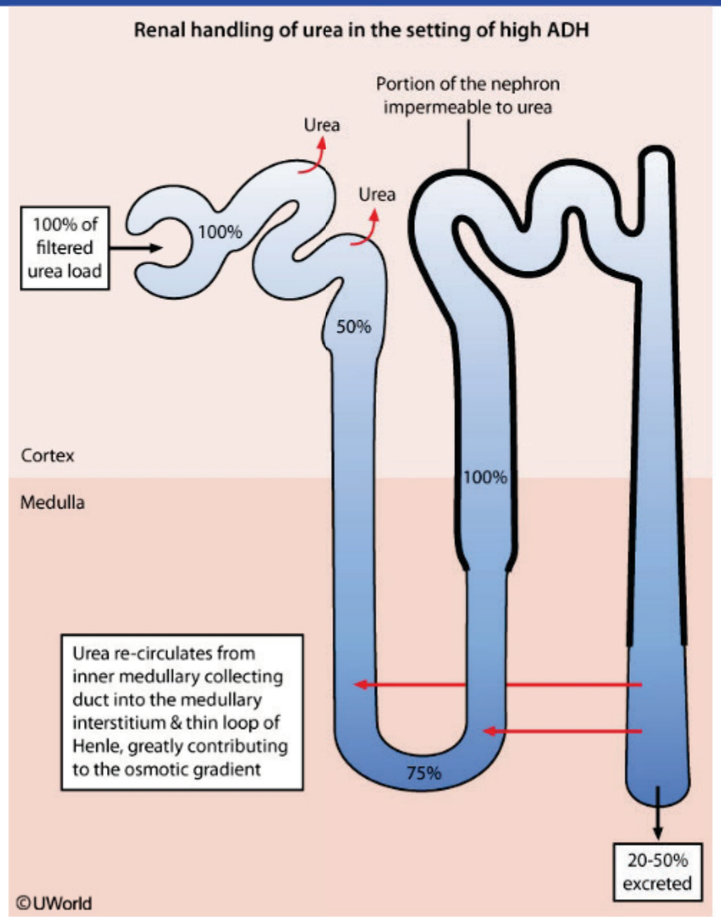
Renal handling of urea in the setting of high ADH



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Polyuria that resolves with the administration of desmopressin (DDAVP, synthetic analogue of vasopressin) is likely secondary to deficient vasopressin secretion (central diabetes insipidus). **Vasopressin** produces a V_2 receptor-mediated increase in water permeability within the cortical and medullary collecting ducts. As water leaves the tubular fluid, urea concentration greatly increases in these tubular segments. Although the cortical collecting duct is impermeable to urea, vasopressin activates urea transporters in the **medullary collecting duct**, increasing urea reabsorption and **decreasing renal urea clearance**. This passive reabsorption of urea into the medullary interstitium in the presence of ADH significantly increases the medullary osmotic gradient, allowing the production of maximally concentrated urine.

(Choice A) The majority of filtered calcium is passively absorbed in the proximal tubule and ascending limb of Henle's loop. Further calcium reabsorption by the distal and collecting ducts is stimulated by parathyroid hormone (not vasopressin).

(Choice B) Creatinine is freely filtered by the glomerulus, and a small amount is also secreted by the proximal tubule. No further secretion or reabsorption occurs beyond the proximal tubule.

(Choice C) Glucose is filtered in the glomerulus and fully reabsorbed in the proximal tubule as long as the filtered glucose is lower than the transport maximum (Tm). Sodium-glucose cotransporter-2 (SGLT-2) receptor inhibitors act on the tubular receptors to lower the Tm of glucose and may be used as third-line agents in type 2 diabetes mellitus.

(Choice D) Para-amino hippuric (PAH) acid is filtered in the glomerulus and nearly completely secreted by the proximal tubules without significant tubular reabsorption. PAH clearance depends on renal plasma flow. Unlike vasopressin, desmopressin selectively activates V_2 receptors and does not cause vasoconstriction (mediated by V_1 receptors).

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Educational objective:
Vasopressin and desmopressin cause a V_2 receptor-mediated increase in water and urea permeability at the inner medullary collecting duct. The resulting rise in urea reabsorption (decreased urea clearance) enhances the medullary osmotic gradient, allowing the production of maximally concentrated urine.

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A 44-year-old man is brought to the hospital after being found unresponsive. Temperature is 35.6 C (96.1 F), blood pressure is 120/80 mm Hg, and pulse is 110/min. He is responsive only to pain and has dry mucous membranes. The patient's condition is initially treated with intravenous fluids, and his mental status slowly improves, but urine output decreases and flank pain develops. A renal biopsy reveals marked ballooning and vacuolar degeneration of proximal renal tubules; multiple oxalate crystals are observed in the tubular lumen. Which of the following is most likely responsible for this patient's acute kidney injury?

- A. Direct tubular injury due to exogenous toxin ingestion
- B. Direct tubular injury from filtered monoclonal light chains
- C. Increased endogenous parathyroid hormone production
- D. Microthrombosis of the glomerular capillaries
- E. Prerenal azotemia due to splanchnic vasodilation

Submit

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- ✓ A. Direct tubular injury due to exogenous toxin ingestion (68%)
- ✗ B. Direct tubular injury from filtered monoclonal light chains (3%)
- C. Increased endogenous parathyroid hormone production (10%)
- D. Microthrombosis of the glomerular capillaries (3%)
- E. Prerenal azotemia due to splanchnic vasodilation (14%)

Incorrect
Correct answer
A

68%
Answered correctly

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Time Spent

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Explanation

This patient has altered mental status and acute renal failure. In conjunction with the oxalate crystals noted on renal biopsy, this presentation is consistent with **ethylene glycol poisoning**. Ethylene glycol is a toxic alcohol found in antifreeze, engine coolants, and brake fluids and may be accidentally or intentionally ingested (used as a substitute for alcohol). Patients initially have symptoms of ethanol intoxication; signs of acute renal failure (oliguria, flank pain) develop approximately 24-72 hours after ingestion. Ethylene glycol itself is relatively nontoxic; however, it is metabolized to glycolic acid and oxalic acid, resulting in its various toxicities

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Acute kidney injury occurs due to both glycolic acid, which causes **direct tubular cytotoxicity**, and oxalic acid, which crystalizes and causes tubular obstruction. This results in **acute tubular necrosis** (ATN), demonstrated histologically by **proximal tubular** cell ballooning and vacuolar **degeneration** with morphologically normal glomeruli. Urinalysis shows tubular casts and oxalate crystals. Other common laboratory findings include a markedly elevated anion gap metabolic acidosis (due to acid metabolite formation) and an elevated osmolar gap (due to the uncharged parent alcohol).

(Choice B) Multiple myeloma can cause light-chain cast nephropathy due to obstruction of the proximal tubules. This causes ATN, but biopsy demonstrates eosinophilic (light-chain) casts, not oxalate crystals. It also typically occurs in older patients and presents with hypercalcemia and anemia; altered mentation is unexpected.

(Choice C) Hyperparathyroidism causes hypercalcemia, which predisposes patients to calcium stone (eg, calcium oxalate) formation. However, kidney stones typically cause postobstructive nephropathy with cortical atrophy and blunting of calyces; ATN would be unexpected.

(Choice D) Thrombotic microangiopathies (eg, hemolytic uremic syndrome) cause endothelial injury characterized by microthrombi in the glomerular capillaries and fibrinoid necrosis of the arterioles; schistocytes are commonly seen on microscopy. Proximal tubules are typically unaffected, and oxalate crystals would not be seen.

(Choice E) Advanced liver disease with portal hypertension and splanchnic vasodilation may lead to renal failure (hepatorenal syndrome). The hallmark of this condition is renal vasoconstriction, resulting in prerenal azotemia.

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(Choice E) Advanced liver disease with portal hypertension and splanchnic vasodilation may lead to renal failure (hepatorenal syndrome). The hallmark of this condition is renal vasoconstriction, resulting in prerenal azotemia. The kidneys are histologically normal and resume function following liver transplantation.

Educational objective:
Ethylene glycol ingestion causes acute tubular necrosis with vacuolar degeneration and ballooning of the proximal tubular cells. Typical clinical findings include altered mentation, renal failure, high anion gap metabolic acidosis, increased osmolar gap, and calcium oxalate crystals in the urine.

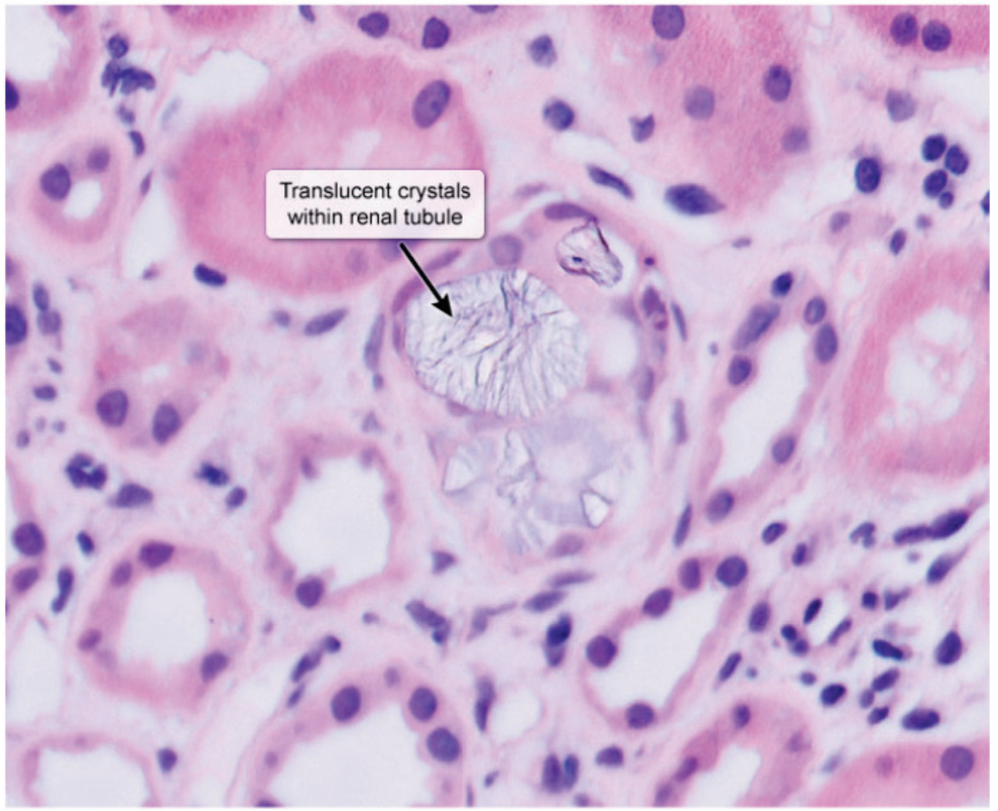
References

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Calcium oxalate crystals



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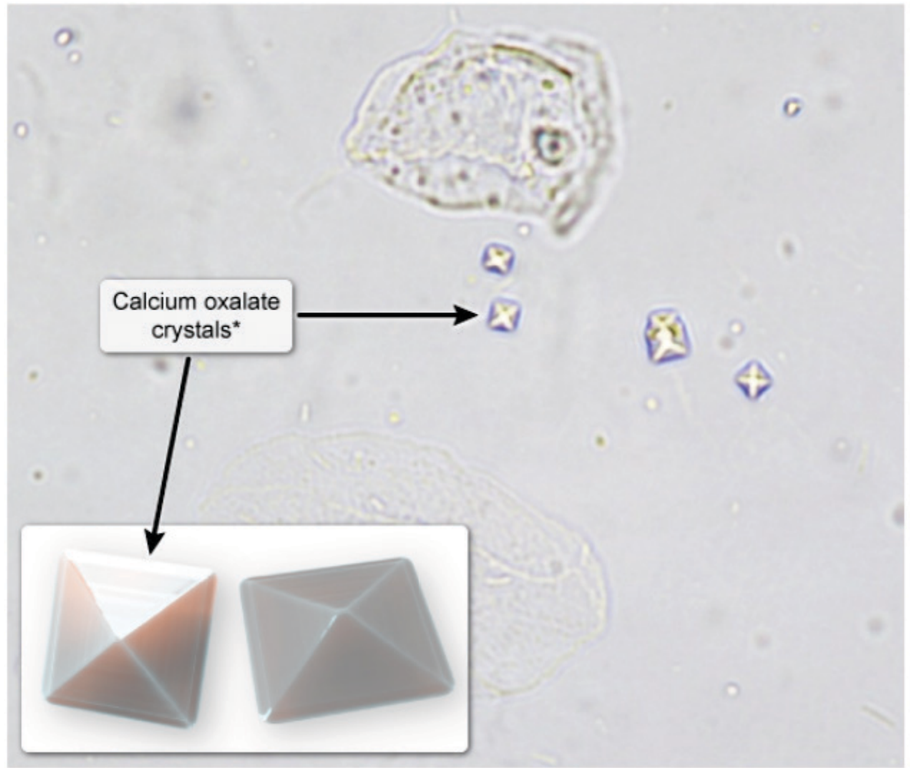
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Calcium oxalate crystals



*Envelope-shaped crystals in urine

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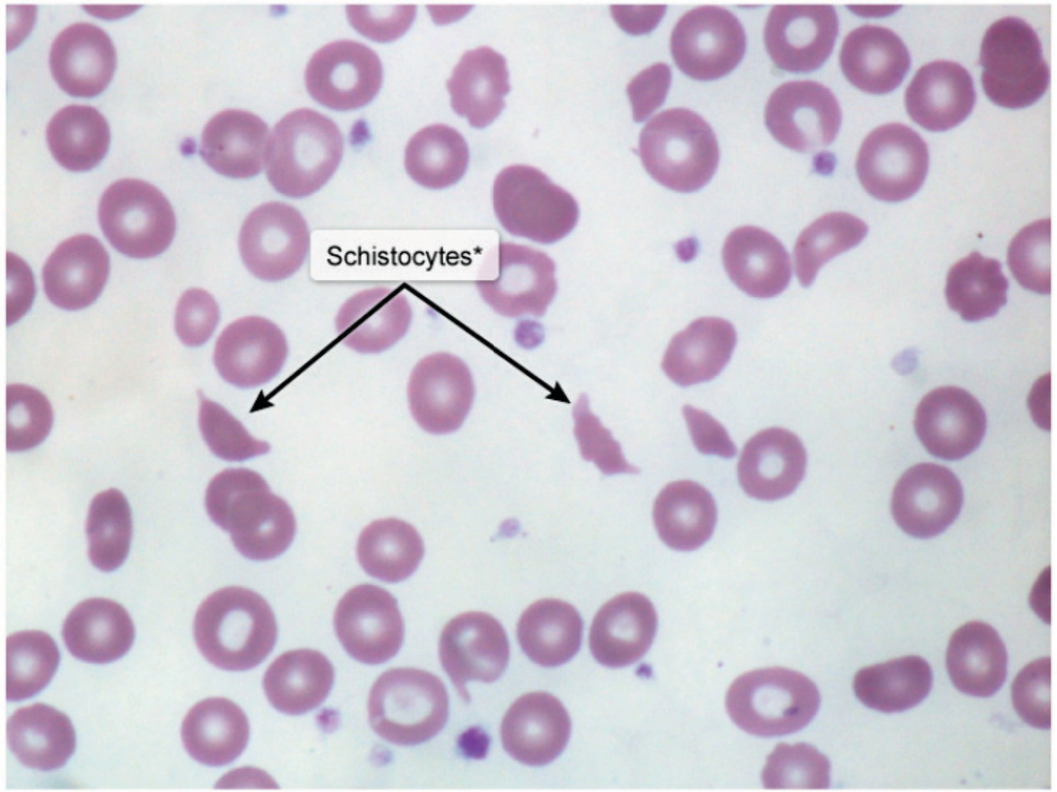
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Schistocytes



*Fragmented red blood cells

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A 45-year-old man with a history of end-stage renal disease undergoes renal allograft transplantation. The donor kidney and proximal ureter are transplanted in the right iliac fossa, with implantation of the ureter into the patient's bladder. Six days following surgery, the donor kidney appears to be functioning well, but the patient develops fever and right lower quadrant abdominal pain. Imaging studies reveal a large pelvic fluid collection. Exploratory laparotomy is performed and discovers urinary leakage, with significant ischemia and necrosis of the transplanted ureter immediately adjacent to the site of implantation into the bladder. The proximal portion of the ureter appears normal. The healthy segment of this patient's transplanted ureter is most likely receiving blood from which of the following arteries?

- A. Common iliac artery
- B. Internal iliac artery
- C. Lumbar arteries
- D. Phrenic artery
- E. Renal artery
- F. Superior vesical artery

Submit

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- ✗ A. Common iliac artery (12%)
- B. Internal iliac artery (22%)
- C. Lumbar arteries (4%)
- D. Phrenic artery (0%)
- ✓ E. Renal artery (50%)
- F. Superior vesical artery (10%)

Incorrect
Correct answer
E

50%
Answered correctly

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Explanation

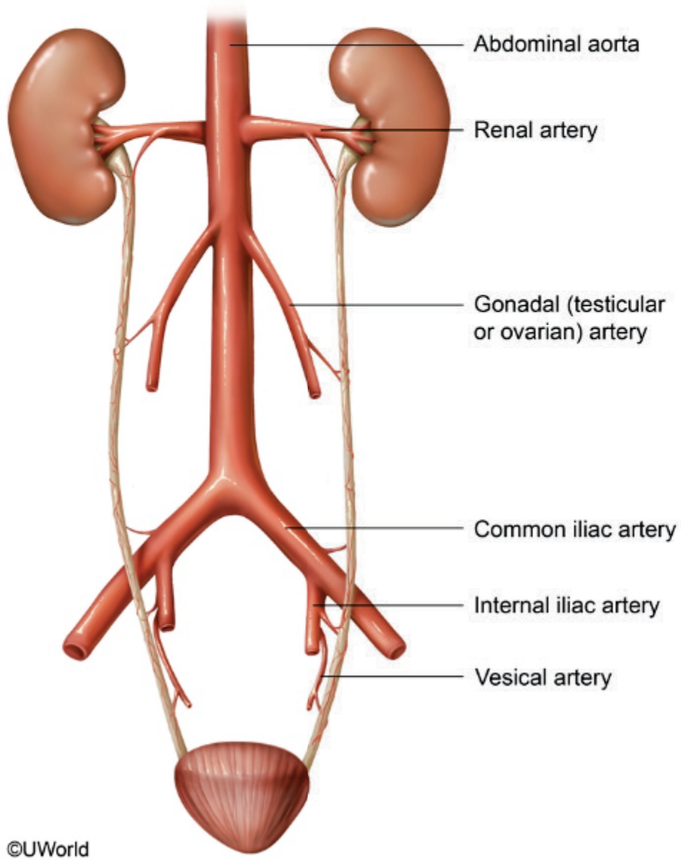
Ureteral circulation

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C. Lumbar arteries (4%)

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Ureteral circulation



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The blood supply to the **proximal ureter** comes from branches of the **renal artery**. At the distal ureter, arterial blood supply arises from the superior vesical artery. In between, the arterial supply to the ureter is anastomotic and highly variable, with possible afferent branches from the gonadal, common and internal iliac, aorta, and uterine arteries.

In a kidney transplant operation, the native kidneys are typically left in place, and the donor kidney is placed retroperitoneally in the right iliac fossa. Blood supply is established by **anastomosing** the **donor renal artery** with the recipient's **external iliac artery**. The proximal 1/3 of the donor ureter is preserved and used to establish continuity from the collecting system of the kidney to the recipient's bladder. Although the transplanted ureter will continue to receive blood through the donor's renal artery, the most distal portion may be susceptible to ischemia due to lack of anastomotic connections. **Distal ureteral ischemia** is a recognized complication of renal transplant and causes leakage of urine 5-10 days following transplant.

(Choices A, B, and F) Branches from the common iliac, internal iliac, and superior vesical arteries supply more distal segments of the ureter, which are not typically retained in the transplanted specimen in order to limit distal ureteral ischemia.

(Choice C) The lumbar arteries arise directly from the aorta to supply the lumbar vertebrae and surrounding structures.

(Choice D) The inferior phrenic arteries are branches of the aorta that supply the diaphragm and provide branches to the suprarenal glands.

Educational objective:
The proximal ureter receives its blood supply from the renal artery whereas the distal ureter is supplied by the superior vesical artery. Circulation to the middle portions of the ureter is variable and anastomotic.

Anatomy | Renal, Urinary Systems & Electrolytes | Ureter injury

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A 76-year-old man comes to the office due to bilateral flank pain and nausea. The patient has not urinated for 24 hours. Medical history is significant for diet-controlled type 2 diabetes and degenerative arthritis of the knee. He occasionally takes naproxen for pain. Temperature is 36.9 C (98.4 F), blood pressure is 140/90 mm Hg, and pulse is 90/min. Cardiopulmonary examination reveals no abnormalities. Abdominal examination shows suprapubic fullness. Mild bilateral costovertebral angle tenderness is present. Laboratory results show a blood urea nitrogen level of 32 mg/dL and creatinine level of 2.6 mg/dL. Four weeks ago, laboratory studies were normal. Which of the following is the most likely cause of this patient's renal dysfunction?

- A. Diabetic nephropathy
- B. Interstitial nephritis
- C. Renal tubule injury due to ischemia
- D. Renal tubule injury due to protein casts
- E. Urethral compression

Submit

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- A. Diabetic nephropathy (6%)
- ✕ B. Interstitial nephritis (18%)
- C. Renal tubule injury due to ischemia (12%)
- D. Renal tubule injury due to protein casts (2%)
- ✓ E. Urethral compression (59%)

Incorrect
Correct answer
E

59%
Answered correctly

05 secs
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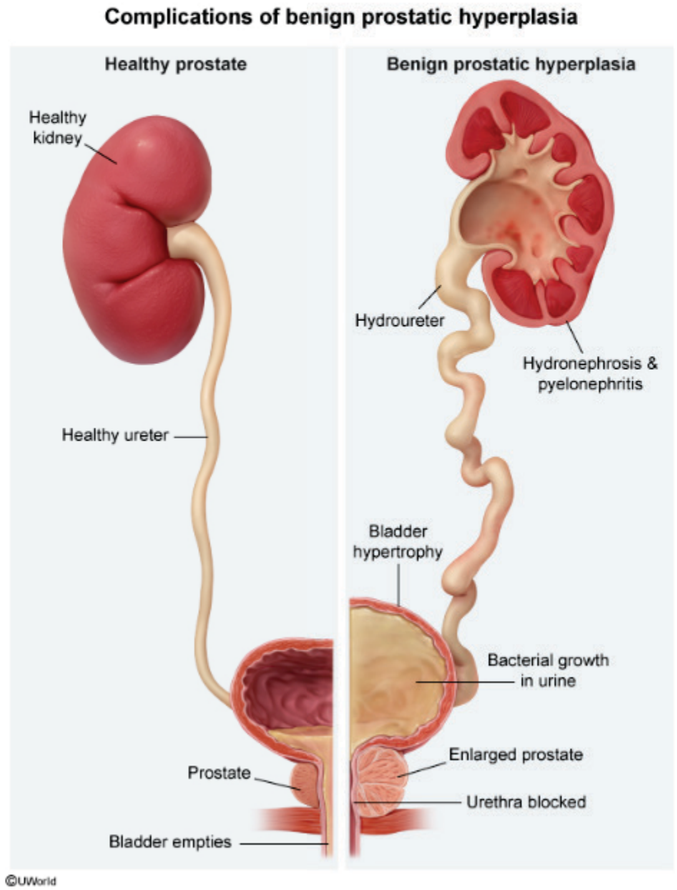
Explanation



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D. Renal tubule injury due to protein casts (2%)

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This patient with **anuria** and **suprapubic fullness** (suggesting a distended bladder) has **acute urinary retention** (AUR). AUR is characterized by the inability to voluntarily micturate, which leads to suprapubic pain with **bladder distension**, often palpable above the pelvic brim. As urine refluxes into the ureters and kidneys, dilation of the ureters, renal pelvis, and calyces (hydronephrosis) results in **acute kidney injury**, bilateral flank pain, and costovertebral angle tenderness. Elevations in creatinine and blood urea nitrogen are also common, but the ratio between the two is variable.

Etiologies of AUR include:

- Bladder outlet obstruction: By far the most common cause of urinary retention, bladder outlet obstructions are precipitated by **urethral compression** typically due to **benign prostatic hyperplasia**, particularly in men age >50. Other etiologies include transitional cell carcinoma and rectal or uterine malignancy.
- Medications: AUR is commonly caused by anticholinergic medications (eg, oxybutynin, atropine) and sympathomimetics (eg, pseudoephedrine).
- Neurologic dysfunction: Diabetic neuropathy, spinal cord injury, and stroke can result in a neurogenic bladder.

(Choice A) Diabetic nephropathy typically presents with proteinuria and chronic kidney disease rather than acute anuria with bilateral flank pain. This patient had normal baseline renal function 4 weeks ago, ruling out chronic kidney disease.

(Choice B) Interstitial nephritis sometimes occurs after the introduction of new medications, such as antibiotics or nonsteroidal anti-inflammatory drugs; however, it is often accompanied by fever and rash, neither of which is present in this patient. In addition, although interstitial nephritis can present with oliguria, an overly distended bladder would not be characteristic.

(Choices C and D) Ischemia (eg, due to hypotension) can cause tubular necrosis. Abundant protein casts can form in multiple myeloma, leading to obstruction and necrosis of the renal tubules. Both cause intrinsic renal injury with an elevation in creatinine; however, a distended bladder would be unexpected.

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Educational objective:
Acute urinary retention is characterized by anuria and bladder distension and can result in hydronephrosis and acute kidney injury. A palpable, distended bladder is present on examination, and abdominal and flank pain may be present. The most common cause of urinary retention is bladder outlet obstruction (urethral compression) due to benign prostatic hyperplasia.

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A 73-year-old man comes to the emergency department with unstable angina. He undergoes coronary angiography via the femoral approach. A stent is placed in the right coronary artery, and the patient is discharged. He returns to the emergency department 2 days later with blue discoloration of his right toe. He has pain and mild tingling in the affected toe. Medical history is significant for hyperlipidemia and coronary artery disease. On physical examination, the right toe appears cyanotic, and there is livedo reticularis affecting the right thigh. Peripheral pulses in the lower extremities are bilaterally palpable. Serum creatinine is 2.8 mg/dL (preoperatively it was 1.0 mg/dL). Which of the following histopathologic findings would most likely be seen on biopsy of this patient's kidney?

- A. Cholesterol clefts in arterial lumen
- B. Glomerular crescent formation
- C. Hyperplastic arteriolar changes
- D. Extensive necrosis of proximal tubular cells
- E. Tubular obstruction with urate crystals

Submit

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- ✓ A. Cholesterol clefts in arterial lumen (41%)
- ✗ B. Glomerular crescent formation (7%)
- C. Hyperplastic arteriolar changes (9%)
- D. Extensive necrosis of proximal tubular cells (33%)
- E. Tubular obstruction with urate crystals (7%)

Incorrect
Correct answer
A

41%
Answered correctly

03 secs
Time Spent

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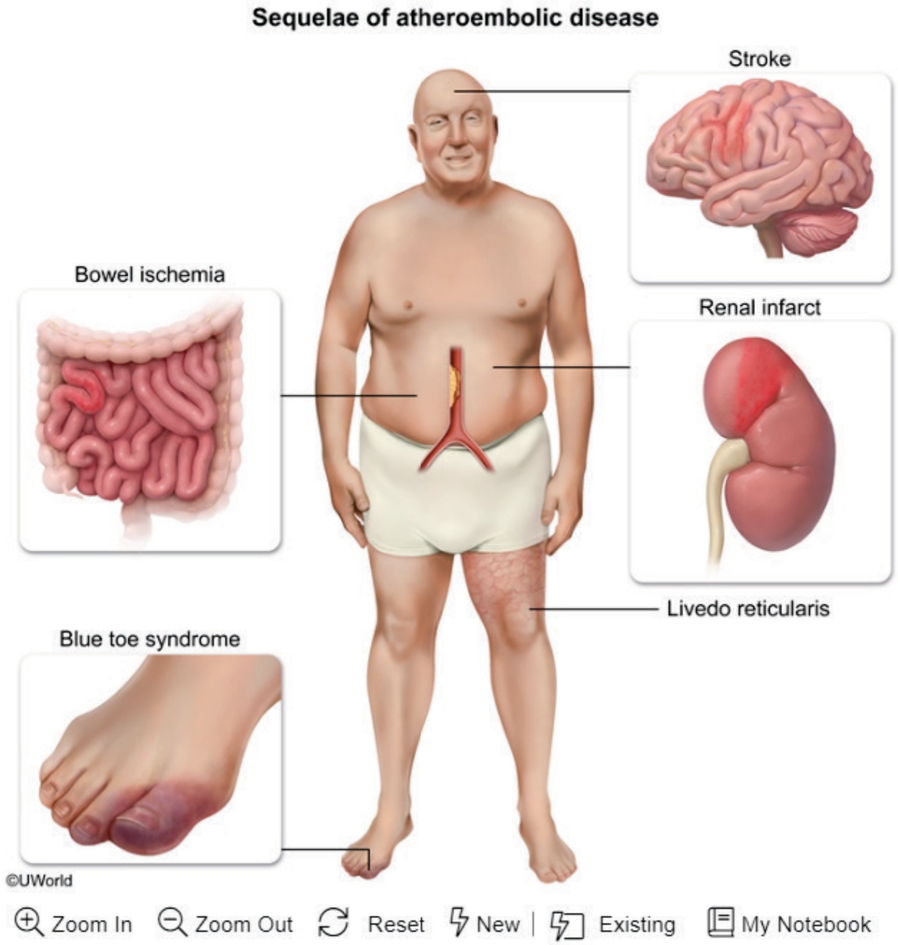
Explanation



https://t.me/USMLEWorldStep1

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This patient has livedo reticularis, a blue toe, and acute kidney injury following coronary angiography; this presentation is concerning for **atheroembolic disease**. Invasive **vascular procedures** (eg, angiography, angioplasty, aortic surgery) can cause cholesterol-containing debris from atherosclerotic plaques to become dislodged from large arteries (eg, the aorta during cardiac catheterization) and shower microemboli into the circulation. These lodge in small, distal arterioles, resulting in ischemia of the corresponding organs and tissues; symptoms develop within a few days or weeks after the procedure. Skin findings (eg, livedo reticularis, blue toe syndrome) are the most common presenting signs. Pulses typically remain palpable as larger arteries are unaffected.

Signs of **acute kidney injury** (eg, oliguria, azotemia) are common in the setting of postprocedure atheroembolism and are frequently seen in elderly patients with preexisting renal atherosclerosis. Frank infarction with flank pain and hematuria does not occur due to the small size of the emboli. Cholesterol is dissolved during tissue preparation for microscopic evaluation, leaving the **needle-shaped clefts** that partially or completely obstruct the arcuate or interlobular renal arteries. Other organs that may be involved are the gastrointestinal tract and the CNS, including the retinal vessels.

(Choice B) Glomerular crescent formation is characteristic of rapidly progressive glomerulonephritis (RPGN). All forms of RPGN have an insidious onset with hematuria, hypertension, and edema.

(Choice C) Hyperplastic arteriolar changes (intimal fibroelastosis) are diagnostic of hypertensive nephropathy seen in patients with poorly controlled hypertension.

(Choice D) Atheroemboli only partially occlude the renal vessels, therefore acute tubular necrosis (ATN) does not typically occur early in the disease process. Complete vessel occlusion with resultant ATN can occur later (weeks to months) due to an endothelial inflammatory response. However, as opposed to toxin-induced ATN (eg, aminoglycosides), which causes diffuse, extensive proximal tubular injury, ischemic ATN typically causes patchy necrosis of the proximal tubules.

(Choice E) Urate nephropathy due to tubular obstruction from urate crystal deposition is usually seen in

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(Choice E) Urate nephropathy due to tubular obstruction from urate crystal deposition is usually seen in individuals with acute hyperuricemia (eg, tumor lysis syndrome). The classic presentation is acute renal failure during chemotherapy for a malignancy.

Educational objective:
Invasive vascular procedures can be complicated by atheroembolic disease, which may involve the kidneys, gastrointestinal tract, CNS, and the skin. Light microscopy shows a partially or completely obstructed arterial lumen with needle-shaped cholesterol clefts within the atheromatous embolus.

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A 5-year-old boy is brought to the office by his mother, who notes that her son's eyes and feet have looked puffy over the last several weeks. She is unaware of exactly when this began but says the patient had a mild upper respiratory tract infection several weeks ago. The boy has no pain but mentions that his shoes seem to fit tightly and bother him, especially when he runs outside during recess at school. The mother also remarks that the boy's urine has been excessively foamy recently. On further questioning, the mother states that she has seasonal allergies and asks whether her child also has allergies. Physical examination is remarkable for periorbital edema and lower extremity edema. Urinalysis shows 4+ proteinuria but is otherwise unremarkable. Which of the following secondary changes is most likely in this patient?

- A. Decreased liver albumin synthesis
- B. Decreased plasma aldosterone level
- C. Increased capillary oncotic pressure
- D. Increased liver lipoprotein synthesis
- E. Increased renal sodium wasting

Submit

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- A. Decreased liver albumin synthesis (8%)
- ✗ B. Decreased plasma aldosterone level (4%)
- C. Increased capillary oncotic pressure (12%)
- ✓ D. Increased liver lipoprotein synthesis (65%)
- E. Increased renal sodium wasting (8%)

Incorrect
Correct answer
D

65%
Answered correctly

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Explanation

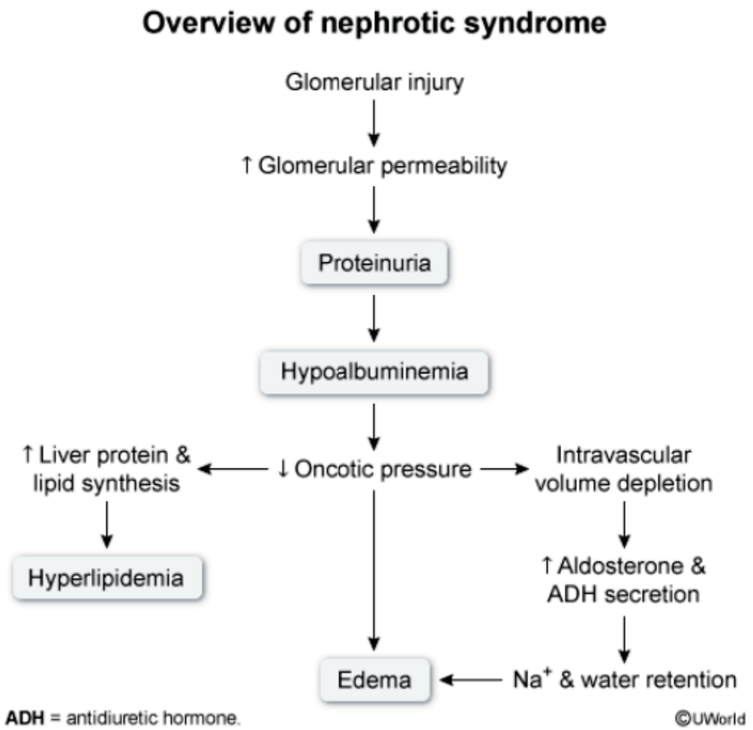
Overview of nephrotic syndrome

Glomerular injury

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E. Increased renal sodium wasting (6%)

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This
typically presents suddenly after an upper respiratory infection. The classic features of nephrotic syndrome are

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This child most likely has minimal change disease, the most common cause of **nephrotic syndrome** in children. It typically presents suddenly after an upper respiratory infection. The classic features of nephrotic syndrome are **heavy proteinuria** (>3.5 g/day in adults and >50 mg/kg/day in children), **hypoalbuminemia** (<3 g/dL), **generalized edema**, and **hyperlipidemia**. Two mechanisms, underfilling and overfilling, contribute to the pathogenesis of edema in nephrotic syndrome. The underfilling mechanism is particularly significant in minimal change disease in children and presents as follows:

1. **Increased glomerular capillary permeability** to plasma proteins leads to massive **loss of protein** (predominantly albumin) in the urine.
2. The large decrease in serum albumin causes a **drop in intravascular oncotic pressure**, which results in fluid moving into the interstitial space and edema formation **(Choice C)**.
3. The fluid shift results in intravascular volume depletion (ie, underfilling), which triggers the renin-angiotensin-aldosterone system to increase aldosterone synthesis (secondary hyperaldosteronism) and antidiuretic hormone secretion **(Choice B)**. The result is intravascular **sodium and water retention (Choice E)**. This fluid leaks back out into the interstitial space due to the low oncotic pressure, exacerbating the edema.
4. Low intravascular oncotic pressure stimulates **increased lipoprotein production** in the liver. Impaired lipid catabolism due to decreased lipoprotein lipase and abnormal transport of circulating lipid particles also contributes to hyperlipidemia.

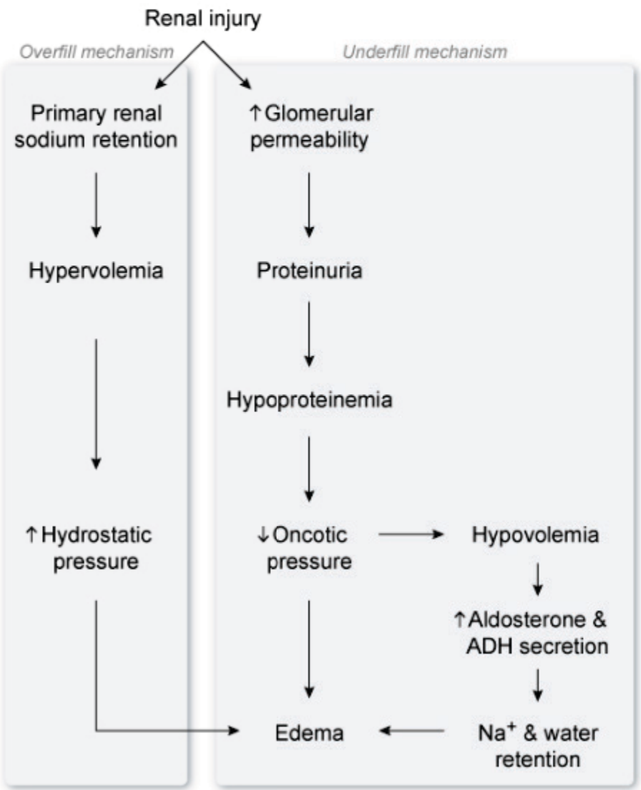
(Choice A) When the serum albumin level decreases due to its massive loss in the urine, the liver responds by increasing albumin synthesis. However, the amount of renal albumin loss exceeds the liver synthetic capacity.

Educational objective:
Minimal change disease is the most common childhood nephrotic syndrome. Increased glomerular capillary permeability causes massive protein (eg, albumin) loss in the urine. Hypoalbuminemia reduces plasma oncotic pressure, which causes a fluid shift into the interstitial space, resulting in edema. Low oncotic pressure also triggers increased lipoprotein production in the liver (ie, hyperlipidemia).

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Exhibit Display

Mechanism of edema formation in nephrotic syndrome



Contribution of each is variable over time & per patient.

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4. Low intravascular oncotic pressure stimulates **increased lipoprotein production** in the liver. Impaired lipid catabolism due to decreased lipoprotein lipase and abnormal transport of circulating lipid particles also

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A 21-year-old man comes to the emergency department due to 1 day of left flank pain and gross hematuria. He reports passage of small blood clots in urine but has had no dysuria or similar symptoms in the past. The patient has no other medical problems and does not take any medications. He does not use tobacco, alcohol, or illicit drugs. His younger sister has sickle cell disease. His temperature is 36.7 C (98 F), blood pressure is 126/70 mm Hg, and pulse is 100/min. Abdominal and genitourinary examination is unremarkable. There is no costovertebral angle tenderness. Which of the following is the most likely cause of this patient's hematuria?

- A. Acute pyelonephritis
- B. Amyloidosis
- C. Fanconi syndrome
- D. Hemolytic-uremic syndrome
- E. Hypersensitivity interstitial nephritis
- F. Ischemic tubular necrosis
- G. Lead nephropathy
- H. Papillary necrosis
- I. Renal artery stenosis
- J. Urate nephropathy

Submit

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- A. Acute pyelonephritis (5%)
- ✗ B. Amyloidosis (1%)
- C. Fanconi syndrome (4%)
- D. Hemolytic-uremic syndrome (9%)
- E. Hypersensitivity interstitial nephritis (4%)
- F. Ischemic tubular necrosis (17%)
- G. Lead nephropathy (0%)
- ✓ H. Papillary necrosis (49%)
- I. Renal artery stenosis (1%)
- J. Urate nephropathy (7%)

Incorrect
Correct answer
H

49%
Answered correctly

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Explanation

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Abrupt-onset gross hematuria in an otherwise healthy patient with a family history of sickle cell disease suggests **renal papillary necrosis (RPN)** due to underlying sickle cell trait. Conditions associated with RPN include:

- **Sickle cell** disease or trait: Sickled cells cause obstruction of small kidney vessels, predisposing to ischemia.
- **Analgesic nephropathy**: Many nonsteroidal anti-inflammatory drugs inhibit renal blood flow by decreasing prostaglandin synthesis and vasoconstricting the afferent arterioles. Certain analgesics can cause ischemia in patients predisposed to renal hypoperfusion.
- Diabetes mellitus: Diabetic metabolic abnormalities (eg, nonenzymatic glycosylation) cause changes in vascular walls, leading to renal vasculopathy and subsequent hypoperfusion.
- Pyelonephritis and urinary tract obstruction: The edematous interstitium of the pyelonephritic kidney compresses the medullary vasculature, leading to ischemia. In this patient, acute pyelonephritis is unlikely in the absence of fever or costovertebral angle tenderness **(Choice A)**.

Gray-white or yellow necrosis of the distal two-thirds of the renal pyramids is seen macroscopically and corresponds microscopically to coagulation necrosis with preserved tubule outlines; cortical surface scars can develop subsequently as inflammatory foci are replaced by fibrous depressions. Symptoms are due to sloughed papillae (sometimes visible in urine as tissue flecks) and include dark or **bloody urine** and colicky **flank pain** (due to ureteral obstruction).

(Choices B and J) Amyloidosis and uric acid nephropathy rarely cause hematuria. Amyloidosis occurs most frequently in the elderly and uric acid nephropathy typically occurs in patients with malignancy (leukemia) or gout.

(Choices C, E, F, G, and I) Fanconi syndrome (polyuria, acidosis, hypophosphatemia), lead nephropathy (Fanconi-like syndrome), hypersensitivity interstitial nephritis (fever, rash, and renal dysfunction due to drug reaction), renal artery stenosis (hypertension in older patients), and acute tubular necrosis (acute kidney injury due to ischemia or nephrotoxins) are not typically characterized by gross hematuria.

(Choice D) Hemolytic-uremic syndrome (microangiopathic hemolytic anemia, thrombocytopenia, acute renal failure) generally occurs 1-2 weeks after a diarrheal illness (classically due to *Escherichia coli* O157:H7)

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patients predisposed to renal hypoperfusion.

- Diabetes mellitus: Diabetic metabolic abnormalities (eg, nonenzymatic glycosylation) cause changes in vascular walls, leading to renal vasculopathy and subsequent hypoperfusion.
- Pyelonephritis and urinary tract obstruction: The edematous interstitium of the pyelonephritic kidney compresses the medullary vasculature, leading to ischemia. In this patient, acute pyelonephritis is unlikely in the absence of fever or costovertebral angle tenderness **(Choice A)**.

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(Choice D) Hemolytic-uremic syndrome (microangiopathic hemolytic anemia, thrombocytopenia, acute renal failure) generally occurs 1-2 weeks after a diarrheal illness (classically due to *Escherichia coli* O157:H7).

Educational objective:
Renal papillary necrosis classically presents with gross hematuria, acute flank pain, and passage of tissue fragments in urine. It is most commonly seen in patients with sickle cell disease or trait, diabetes mellitus, analgesic nephropathy, or severe obstructive pyelonephritis.

References

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A 21-year-old health care worker with a history of bulimia nervosa is brought to the hospital due to generalized weakness and dizziness. She reports no vomiting or laxative use. On admission, she is fully responsive. Blood pressure is 110/60 mm Hg and pulse is 102/min. Physical examination shows dry mucous membranes. Urine screening for diuretics reveals a large amount of furosemide. Which of the following sets of laboratory findings would most likely suggest that this patient is abusing furosemide to lose weight?

	Serum bicarbonate	Serum chloride	Urine sodium	Urine potassium
○ A.	↑	↓	↑	↑
○ B.	↓	↓	↑	↑
○ C.	↓	Normal	Normal	↓
○ D.	↓	↓	↑	↓
○ E.	↑	↑	Normal	↑

Submit

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	Serum bicarbonate	Serum chloride	Urine sodium	Urine potassium	
✓ A.	↑	↓	↑	↑	(68%)
✗ B.	↓	↓	↑	↑	(15%)
C.	↓	Normal	Normal	↓	(1%)
D.	↓	↓	↑	↓	(6%)
E.	↑	↑	Normal	↑	(7%)

Incorrect
Correct answer
A

68%
Answered correctly

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Time Spent

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Explanation

Hypokalemic, hypochloremic metabolic alkalosis	
Common etiologies	• Gastric suction or severe vomiting • Loop or thiazide diuretic overuse

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Hypokalemic, hypochloremic metabolic alkalosis	
Common etiologies	• Gastric suction or severe vomiting • Loop or thiazide diuretic overuse
Pathophysiology	• Gastric or renal H^+ losses **initiate** alkalosis • Volume depletion activates RAAS • ↑ Renal K^+ & H^+ losses cause hypokalemia & **worsen** alkalosis • Relatively greater loss of Cl^- than Na^+ → profound Cl^- depletion • ↓ Cl^- impairs renal HCO_3^- excretion to **perpetuate** alkalosis
Management	• Remove or treat initiating factor • Cl^- replenishment with normal saline corrects alkalosis
RAAS = renin-angiotensin-aldosterone system.	

Loop diuretics (eg, furosemide) are sometimes abused by patients with eating disorders (eg, anorexia nervosa, bulimia nervosa) in an effort to lose weight. These drugs **inhibit the Na^+-K^+-2Cl^- transporter** in the loop of Henle, resulting in increased urinary excretion of Na^+, Cl^-, K^+, and water. These changes in electrolyte handling also increase renal H^+ excretion, leading to **metabolic alkalosis** (elevated serum HCO_3^-). Overuse of loop diuretics leads to massive electrolyte and fluid losses with **intravascular volume depletion** and activation of the renin-angiotensin-aldosterone system. This secondary hyperaldosteronism stimulates increased Na^+ reabsorption in the renal tubular collecting duct, as well as a lesser degree of passive Cl^- reabsorption. The relatively high loss of Cl^-

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Secondary hyperaldosteronism also stimulates increased K^+ and H^+ excretion in the collecting duct, exacerbating the **hypokalemia** and metabolic alkalosis. The alkalosis is further compounded by an angiotensin II-mediated increase in proximal tubule sodium bicarbonate reabsorption. **Chloride depletion** then **perpetuates the alkalosis** because low Cl^- levels in the tubular lumen impair HCO_3^- excretion via the pendrin Cl^-/HCO_3^- exchanger on beta intercalated cells in the collecting duct.

The **urine electrolyte** findings in loop diuretic abuse depend on how recently the medication was last ingested. Within several hours after ingestion (as in this patient with positive urine screening), **increased urine Na^+, Cl^-, and K^+** is expected. Once the medication effect wears off, urine Na^+ and urine Cl^- are low as the kidneys attempt to increase blood volume. Urine K^+ is likely to remain increased due to ongoing aldosterone-mediated losses **(Choice C)**.

(Choices B, D, and E) Because Cl^- and HCO_3^- are the most abundant anions in the body, they are the primary determinants of total body electronegativity. Therefore, when one of these anions is depleted the kidneys and intestines retain the other to maintain electronegative balance. This results in a typical inverse relationship between serum Cl^- and serum HCO_3^- levels (when one is low the other tends to be elevated). The presence of additional anions in the body (eg, anion gap metabolic acidosis) may disrupt this relationship.

Educational objective:

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leads to massive electrolyte and fluid losses with **intravascular volume depletion** and activation of the renin-angiotensin-aldosterone system. This secondary hyperaldosteronism stimulates increased Na^+ reabsorption in the renal tubular collecting duct, as well as a lesser degree of passive Cl^- reabsorption. The relatively high loss of Cl^- that occurs is responsible for a **characteristic hypochloremia**.

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Educational objective:
Overuse or abuse of loop diuretics (eg, furosemide) characteristically causes hypokalemic, hypochloremic metabolic alkalosis. Urine electrolyte findings depend on how recently the diuretic was last ingested; increased urine Na^+, Cl^-, and K^+ are expected with recent ingestion.

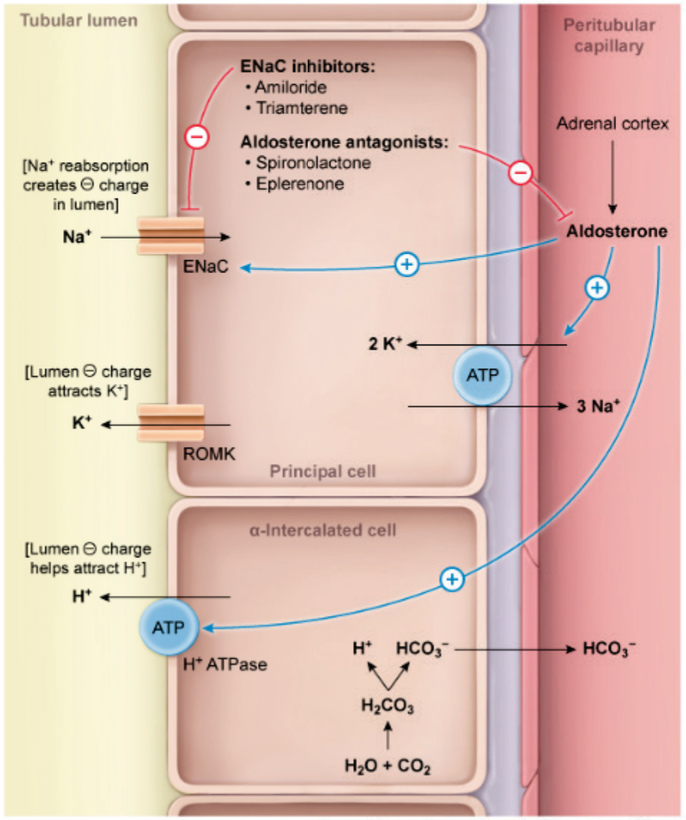
References

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RAAS = renin-angiotensin-aldosterone system.

Exhibit Display

Action of aldosterone in the collecting duct of the nephron



ENaC = epithelial sodium channel; **ROMK** = renal outer medullary potassium channel. ©UWorld

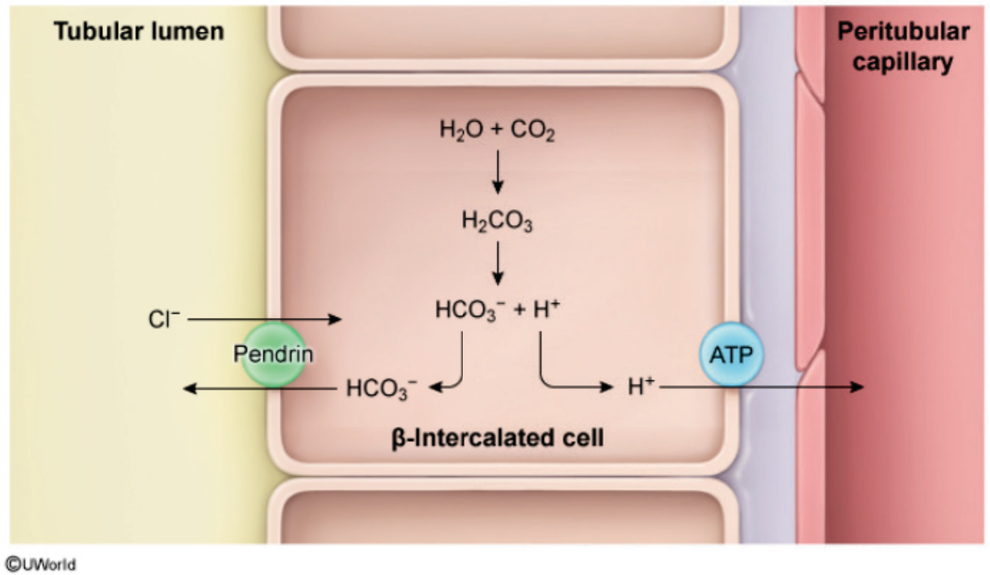
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RAAS = renin-angiotensin-aldosterone system.

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A 5-year-old boy is brought to the office with generalized edema that developed following a mild upper respiratory infection. Medical history is unremarkable. Blood pressure and heart rate are normal. Serum creatinine levels are normal. Urinalysis shows massive proteinuria with no hematuria. Further analysis reveals that urine protein consists principally of albumin with only trace amounts of IgG and alpha-2-macroglobulin. Which of the following pathologic changes is the most likely cause of this patient's urinary protein loss?

- A. Glomerular crescent formation
- B. Loss of glomerular basement membrane anions
- C. Nodular glomerulosclerosis
- D. Thinning of the glomerular basement membrane
- E. Tubular necrosis and epithelial shedding

Submit

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- A. Glomerular crescent formation (3%)
- ✓ B. Loss of glomerular basement membrane anions (77%)
- C. Nodular glomerulosclerosis (3%)
- D. Thinning of the glomerular basement membrane (13%)
- E. Tubular necrosis and epithelial shedding (1%)

Correct

77% Answered correctly

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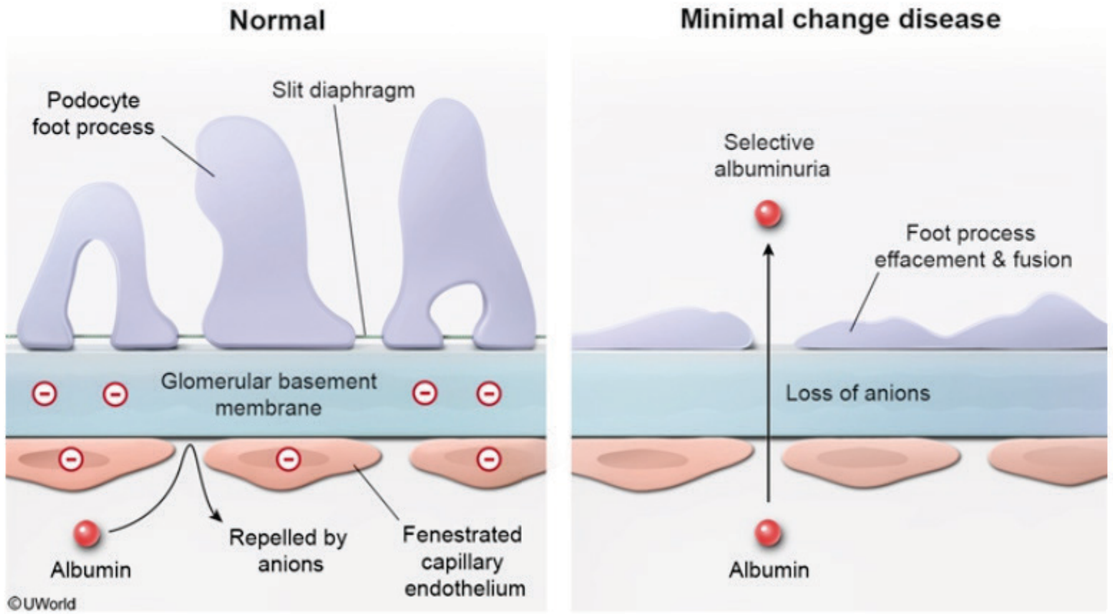
Explanation



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E. Tubular necrosis and epithelial shedding (1%)

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dysfunction leads to overproduction of a **glomerular permeability factor** (possibly IL-13) that directly **damages**

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This pediatric patient presenting with generalized edema and massive proteinuria following an upper respiratory infection likely has **minimal change disease**, the most common cause of nephrotic syndrome in children.

Minimal change disease is caused by **immune dysregulation**, as suggested by its association with respiratory infections, immunizations, and atopic disorders, as well as its excellent response to corticosteroids. Immune dysfunction leads to overproduction of a **glomerular permeability factor** (possibly IL-13) that directly **damages podocytes**, leading to foot process effacement and fusion as well as decreased anionic properties of the glomerular basement membrane. **Loss of negative charge** leads to selective loss of albumin in the urine (**selective albuminuria**), in contrast to the nonselective proteinuria seen with other forms of nephrotic syndrome (eg, membranous nephropathy, focal segmental glomerulosclerosis).

Despite the dramatic clinical picture, light microscopy and immunofluorescence studies show completely normal kidneys; the characteristic effacement of the podocyte foot processes can be detected only by electron microscopy.

(Choice A) Crescent formation is a sign of severe glomerular injury; it is associated with rapidly progressive glomerulonephritis (RPGN), which can occur secondary to multiple diseases (eg, anti–glomerular basement membrane disorder, antineutrophil cytoplasmic antibody vasculitides). However, RPGN typically presents with renal insufficiency and nephritic urine sediment (ie, hematuria, red blood cell casts); massive proteinuria would be unexpected.

(Choice C) Nodular glomerulosclerosis (Kimmelstiel-Wilson lesions) occurs in patients with diabetic nephropathy and is characterized by ovoid nodules of hyaline material within the mesangium. Although diabetic nephropathy may present as nephrotic syndrome, patients are typically middle-aged to elderly with a long history of diabetes mellitus.

(Choice D) Thinning of the glomerular basement membrane is seen in thin basement membrane nephropathy and Alport syndrome. Thin basement membrane nephropathy is a benign condition typically associated with microscopic hematuria. Alport syndrome is caused by an inherited defect in the formation of type IV collagen;

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(eg, membranous nephropathy, focal segmental glomerulosclerosis).

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(Choice D) Thinning of the glomerular basement membrane is seen in thin basement membrane nephropathy and Alport syndrome. Thin basement membrane nephropathy is a benign condition typically associated with microscopic hematuria. Alport syndrome is caused by an inherited defect in the formation of type IV collagen; patients have hearing loss, ocular abnormalities, hematuria, and progressive renal insufficiency.

(Choice E) Focal tubular epithelial necrosis and cell shedding occur in acute tubular necrosis, which typically follows renal ischemia or exposure to nephrotoxins (eg, aminoglycosides). It manifests as acute renal injury with muddy brown casts, not nephrotic syndrome.

Educational objective:
Minimal change disease is caused by immune dysregulation and overproduction of a glomerular permeability factor, which damages podocytes and decreases the anionic properties of the glomerular basement membrane. This results in selective loss of albumin in the urine, in contrast to the nonselective proteinuria seen in other forms of nephrotic syndrome.

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Exhibit Display

Nephritic vs nephrotic syndrome		
	Nephritic	**Nephrotic**
Proteinuria	Mild	Significant (>3.5 g/day)
Serum albumin	Normal	Decreased
Edema	Mild	Significant
GFR	Decreased	Normal
Hypertension	Yes	No
Hematuria	Yes	No
Pyuria	Yes	No
Casts	RBC	Fatty or none
GFR = glomerular filtration rate; **RBC** = red blood cell.		

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This pediatric patient presenting with generalized edema and massive proteinuria following an upper respiratory infec

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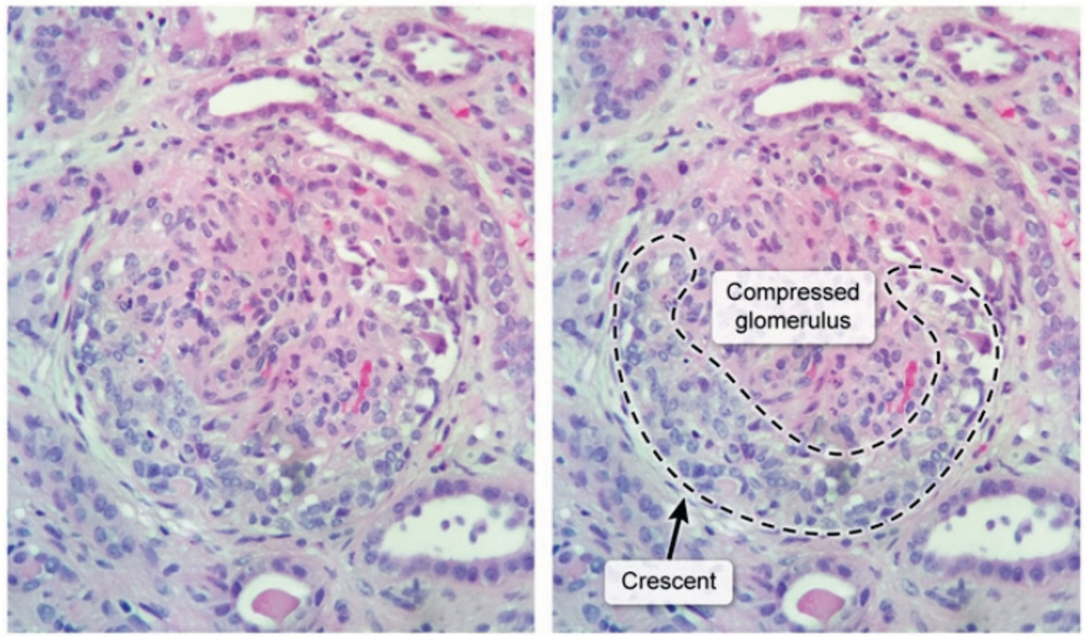
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microscopic hematuria. Alport syndrome is caused by an inherited defect in the formation of type IV collagen;

Exhibit Display

Crescentic glomerulonephritis



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A 32-year-old man comes to the emergency department due to sudden onset of severe right flank pain that radiates toward the groin. He also has gross hematuria but no fever or dysuria. The patient has no significant medical conditions and has never experienced similar symptoms. He takes no medications. Temperature is 36.7 C (98.1 F), blood pressure is 120/80 mm Hg, and pulse is 88/min. The right flank is tender to palpation. There is no costovertebral angle tenderness. Imaging shows a stone in the middle of the right ureter. Which of the following is most likely to be seen on laboratory evaluation of this patient?

- A. Hypercalcemia, hypercalciuria
- B. Hyperuricemia, hyperuricosuria
- C. Normocalcemia, hypercalciuria
- D. Normocalcemia, hyperoxaluria
- E. Normouricemia, hyperuricosuria

Submit

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- ✗ A. Hypercalcemia, hypercalciuria (13%)
- B. Hyperuricemia, hyperuricosuria (2%)
- ✓ C. Normocalcemia, hypercalciuria (62%)
- D. Normocalcemia, hyperoxaluria (19%)
- E. Normouricemia, hyperuricosuria (2%)

Incorrect
Correct answer
C

62%
Answered correctly

05 secs
Time Spent

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Explanation

Calcium stones represent 75%-80% of all renal calculi and include calcium oxalate and calcium phosphate stones. **Hypercalciuria** is the most common risk factor for calcium stones in adults.

In most patients, the hypercalciuria is **idiopathic**. Factors can include increased gastrointestinal absorption, increased mobilization of calcium from bone, or decreased renal tubular calcium reabsorption. However, in the absence of an underlying metabolic disorder (eg, hyperparathyroidism), most patients remain **normocalcemic** due

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(Choice A) Hypercalcemia with resulting hypercalciuria may occur in primary hyperparathyroidism, sarcoidosis, malignancy, and chronic acidemia. However, these are less common causes of nephrolithiasis, and this patient has no symptoms of hypercalcemia (eg, fatigue, constipation) or clinical features to suggest a disorder that might cause hypercalcemia.

(Choices B and E) Hyperuricosuria with hyperuricemia can occur with myeloproliferative disorders, tumor lysis syndrome, gout, and Lesch-Nyhan syndrome. High-protein diets typically cause hyperuricosuria with normouricemia. Hyperuricosuria can cause uric acid stone formation and also predisposes to calcium nephrolithiasis (uric acid precipitation acts as a nidus for calcium deposition).

(Choice D) Hyperoxaluria can result from a diet high in oxalate (found in foods such as chocolate, nuts, and spinach). Low-calcium diets and intestinal malabsorption syndromes such as Crohn disease can also cause hyperoxaluria as both cause less calcium to be available to bind and trap oxalate in the gut. Hyperoxaluria is a less common risk factor for calcium stone formation than hypercalciuria.

Educational objective:
Hypercalciuria is the most common risk factor for calcium (calcium oxalate and calcium phosphate) kidney stones in adults; contributing factors may include increased gastrointestinal absorption, increased mobilization of calcium from bone, or decreased renal tubular calcium reabsorption. However, most patients remain normocalcemic due to regulation of plasma calcium levels by vitamin D and parathyroid hormone.

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A 55-year-old man is evaluated due to worsening fatigue and exertional shortness of breath. He has no chronic medical conditions and takes no medications. Physical examination shows facial puffiness and bilateral lower extremity edema. Urinalysis shows 3+ proteinuria. Kidney biopsy findings with special staining under polarized light are shown on the image below:

Which of the following tests would be most helpful for establishing a specific diagnosis in this patient?

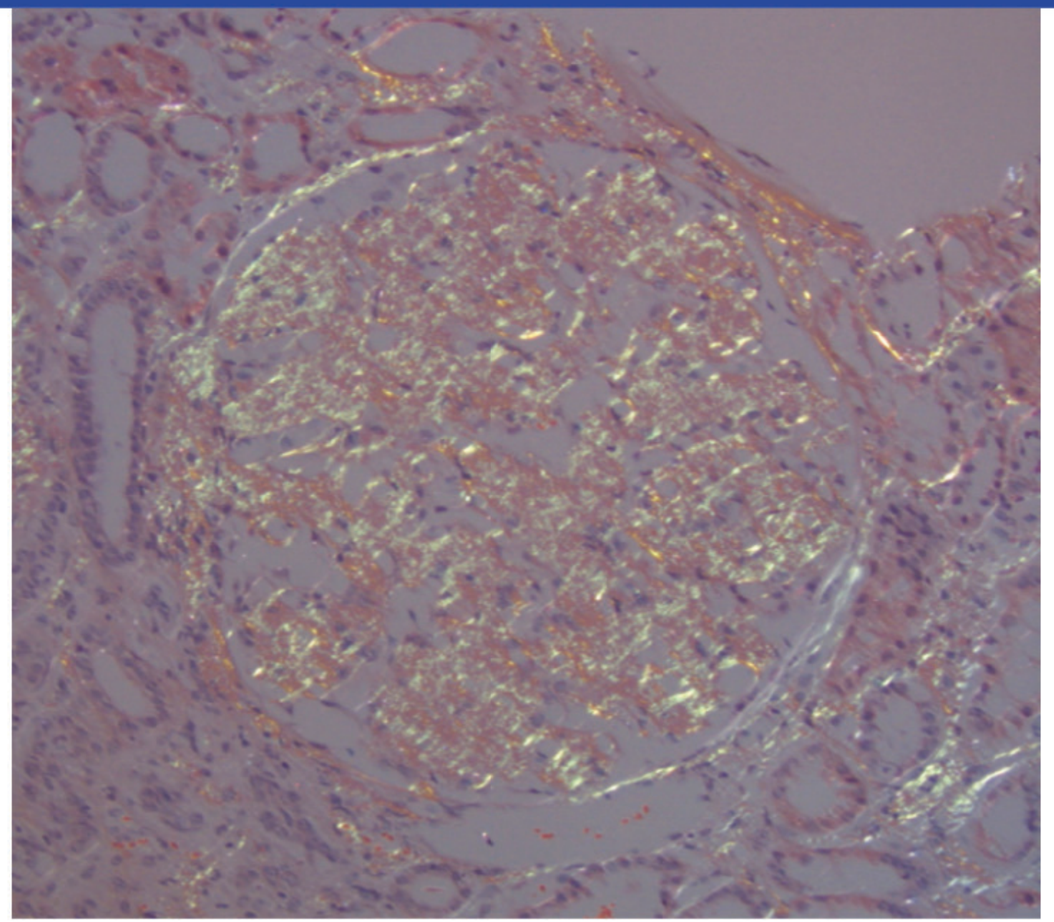
- A. 24-hour urinary copper excretion
- B. 24-hour urinary uric acid excretion
- C. Serum protein electrophoresis
- D. Serum total bilirubin concentration
- E. Serum total body iron content

Submit

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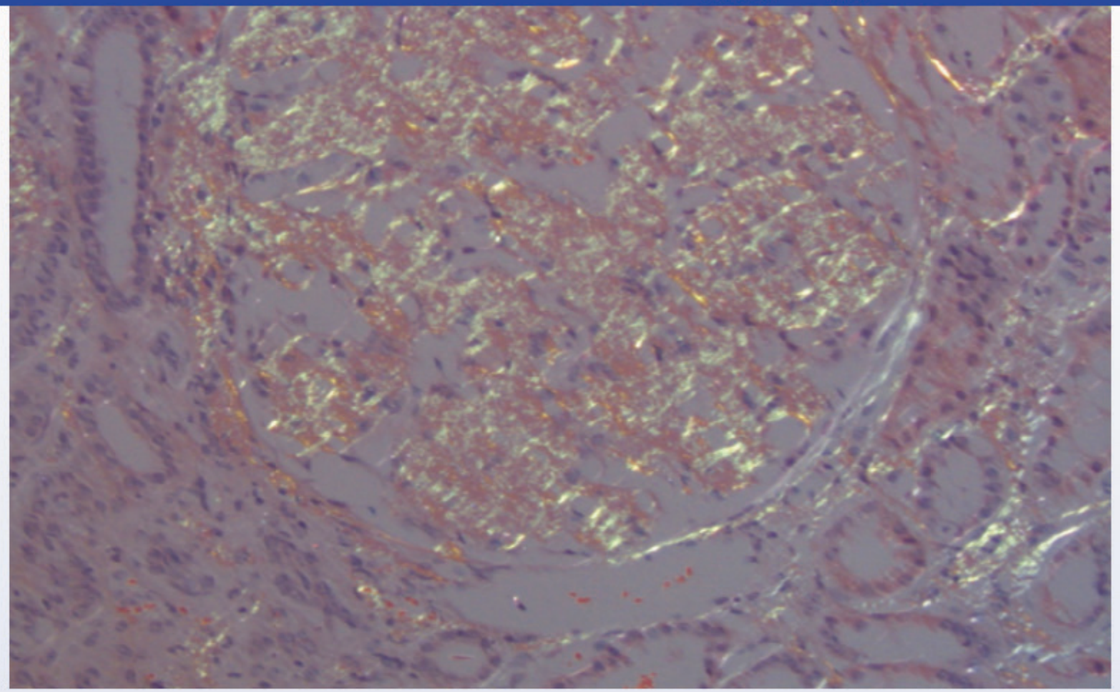
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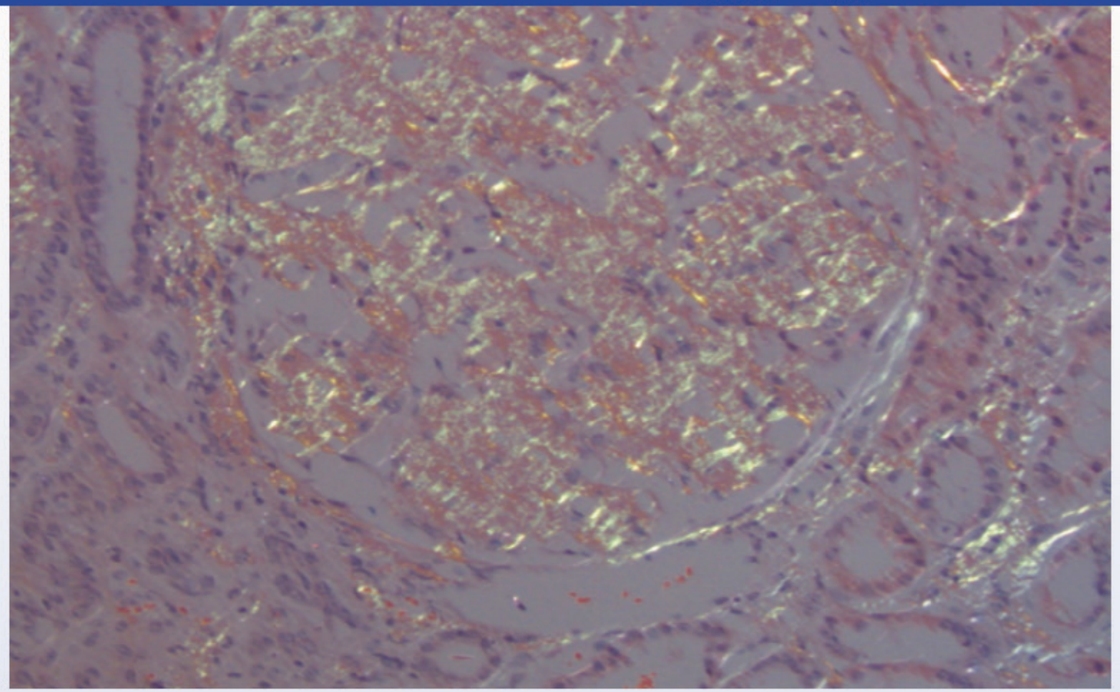


Which of the following tests would be most helpful for establishing a specific diagnosis in this patient?

- A. 24-hour urinary copper excretion
- B. 24-hour urinary uric acid excretion
- C. Serum protein electrophoresis
- D. Serum total bilirubin concentration
- E. Serum total body iron content

Submit

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Which of the following tests would be most helpful for establishing a specific diagnosis in this patient?

- A. 24-hour urinary copper excretion (14%)
- ✕ B. 24-hour urinary uric acid excretion (11%)
- ✓ C. Serum protein electrophoresis (62%)
- D. Serum total bilirubin concentration (2%)
- E. Serum total body iron content (8%)

Incorrect
Correct answer
C

62%
Answered correctly

12 secs
Time Spent

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Version

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Major types of systemic amyloidosis

	Primary	Secondary	Age related	Dialysis related
Disease association	Plasma cell dyscrasia	Chronic infection/ inflammation	Elderly men	ESRD on dialysis
Precursor protein ↓ **Misfolding mechanism** ↓ **Amyloid fibril type**	Immunoglobulin light chains ↓ Increased production ↓ AL	Serum amyloid A ↓ Increased production ↓ AA	Transthyretin (prealbumin) ↓ Accumulation over time ↓ ATTR*	β_2-Microglobulin ↓ Decreased clearance ↓ $A\beta_2M$
Clinical manifestations	Nephropathy, hepatosplenomegaly, cardiomyopathy (AL > AA), peripheral neuropathy, macroglossia, skin bruising		Cardiomyopathy, CTS, other peripheral neuropathy	Scapulohumeral arthritis, CTS

Amyloid names begin with "A" followed by the precursor protein abbreviation.
*ATTR also occurs in a hereditary form that affects younger patients.
CTS = carpal tunnel syndrome; **ESRD** = end-stage renal disease.

This patient with heavy (ie, 3+) proteinuria and peripheral edema has **nephrotic syndrome**. His kidney biopsy shows **apple-green birefringence** under polarized light (with specialized Congo red staining), which is pathognomonic for amyloidosis.

Amyloidosis is a disorder of protein folding. Misfolded proteins form **insoluble fibrils**, resulting in extracellular deposition that causes **organ dysfunction**. The parallel fibril alignment binds to Congo red in a regular manner

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Amyloidosis is a disorder of protein folding. Misfolded proteins form **insoluble fibrils**, resulting in extracellular deposition that causes **organ dysfunction**. The parallel fibril alignment binds to Congo red in a regular manner that produces the birefringence seen on polarized microscopy. Multiple precursor proteins can lead to amyloid fibril formation and can cause differing clinical manifestations based on the location of deposition.

Renal amyloid deposits result in glomerular damage, producing proteinuria, typically in the nephrotic range. The most common precursor proteins causing kidney injury are serum amyloid A (AA amyloidosis) and immunoglobulin light chains **(AL amyloidosis)**. Serum amyloid A is an acute phase reactant; AA amyloidosis usually occurs in patients with chronic inflammatory conditions (unlike this patient). Therefore, **serum protein electrophoresis** would be helpful to look for a monoclonal protein produced by an undiagnosed plasma cell dyscrasia (eg, multiple myeloma, Waldenstrom macroglobulinemia) causing AL amyloidosis.

(Choice A) 24-hour urinary copper excretion is elevated in Wilson disease, which typically presents with hepatic, neurologic, and psychiatric abnormalities. Renal involvement is less common and causes tubular (eg, Fanconi syndrome) rather than glomerular dysfunction.

(Choice B) 24-hour urinary uric acid excretion is useful for evaluating disorders with hyperuricemia (eg, gout, kidney stones). Uric acid crystals share the property of birefringence on polarized microscopy. However, nephrotic syndrome would be unexpected even with chronic urate nephropathy.

(Choice D) Serum total bilirubin concentration is elevated in multiple disorders and can result from overproduction, impaired conjugation, biliary obstruction, or hepatocyte damage. It has no role in determining the type of amyloidosis causing nephrotic syndrome.

(Choice E) Serum total body iron content is indicated for the assessment of anemia and iron overload, neither of

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formation and can cause differing clinical manifestations based on the location of deposition.

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(Choice D) Serum total bilirubin concentration is elevated in multiple disorders and can result from overproduction, impaired conjugation, biliary obstruction, or hepatocyte damage. It has no role in determining the type of amyloidosis causing nephrotic syndrome.

(Choice E) Serum total body iron content is indicated for the assessment of anemia and iron overload, neither of which is associated with nephrotic syndrome. Liver biopsy is sometimes performed for iron overload, which shows intense staining with Prussian blue.

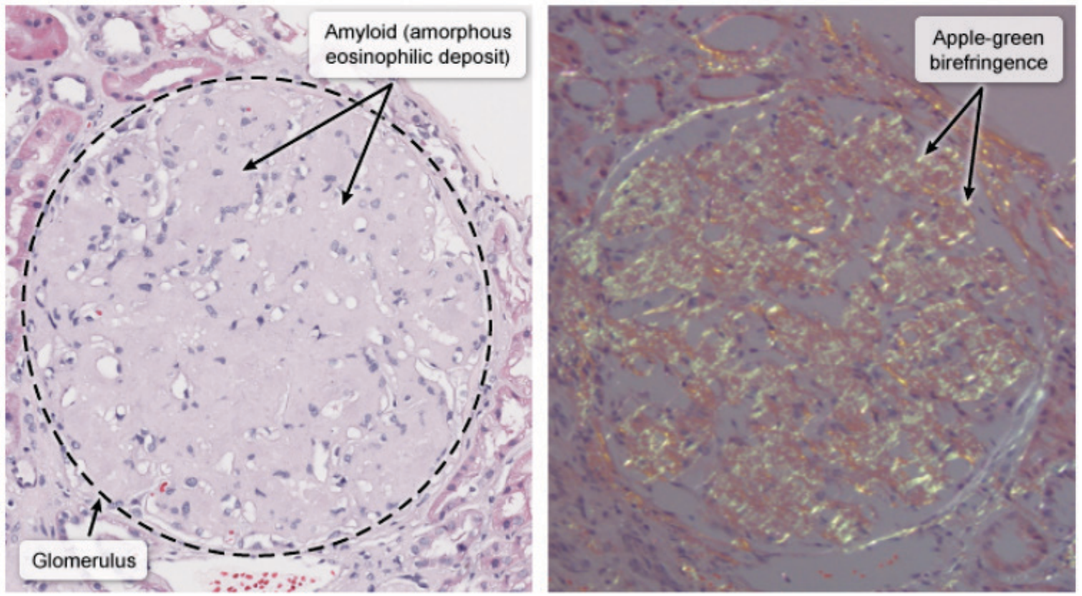
Educational objective:
Renal amyloidosis typically presents with proteinuria and nephrotic syndrome. The diagnosis is confirmed by kidney biopsy showing apple-green birefringence with Congo red stain under polarized light. Serum protein electrophoresis demonstrating a monoclonal protein helps establish the diagnosis of immunoglobulin light chain (AL) amyloidosis.

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fibril type	AL	AA	ATTR	

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Renal amyloidosis



Hematoxylin & eosin stain

Congo red stain under polarized light

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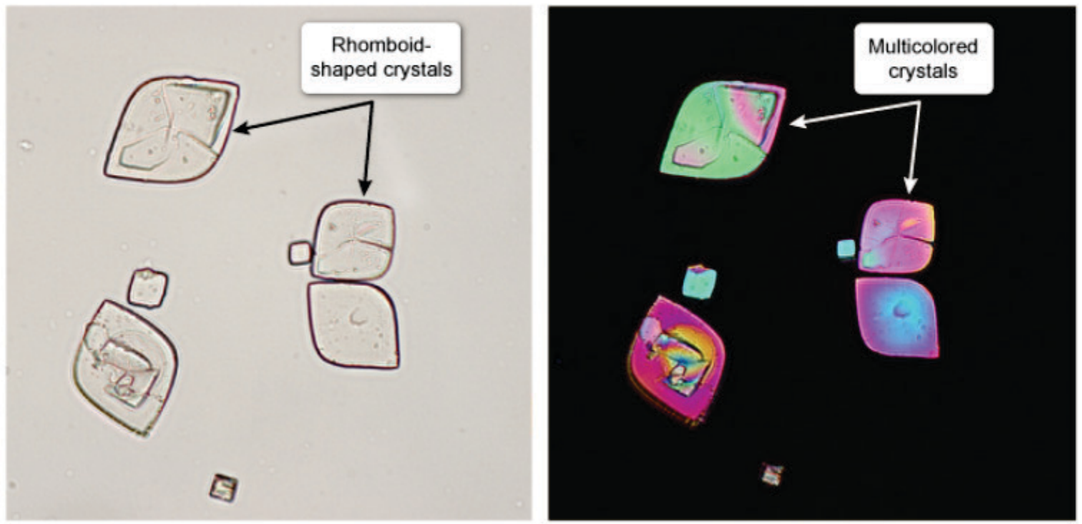
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Uric acid crystals



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Urine sediment

Urine sediment under polarized light

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https://t.me/USMLEWorldStep1

patients with chronic inflammatory conditions (unlike this patient). Therefore, **serum protein electrophoresis**

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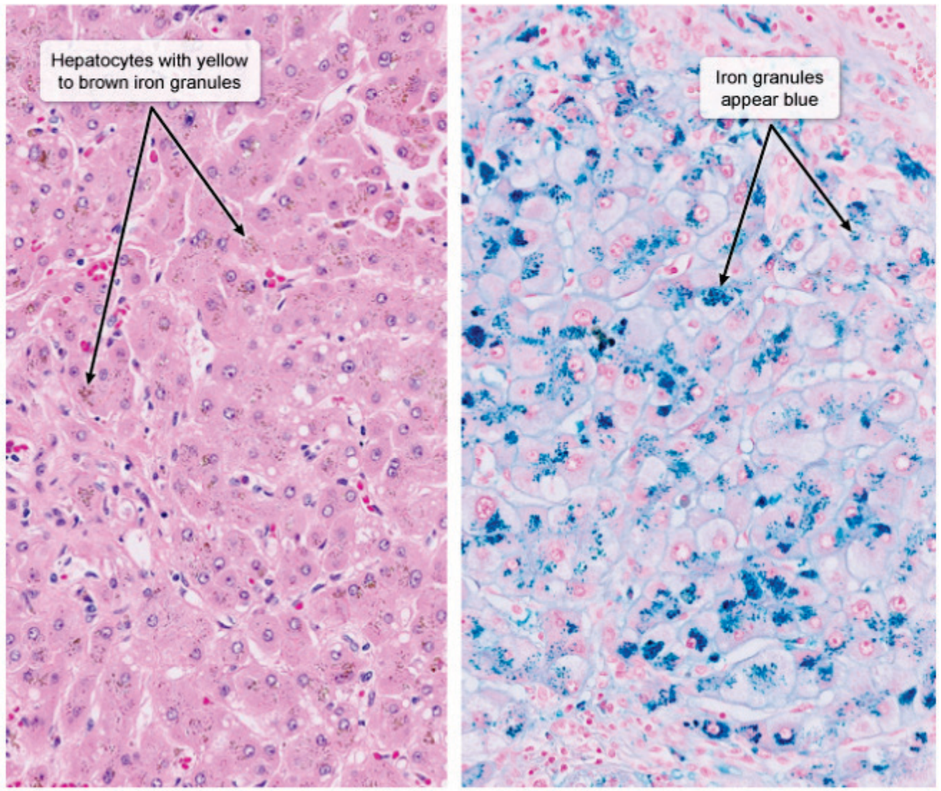
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Exhibit Display

Hereditary hemochromatosis



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Hematoxylin & eosin stain

Prussian blue stain

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A 54-year-old woman is brought to the hospital due to fever, nausea, vomiting, and confusion. For the past 3 days, she has had dysuria and increased frequency of urination. Medical history is significant for recurrent urinary tract infections and primary hypertension. Family history is insignificant. Temperature is 39.2 C (102.6 F), blood pressure is 90/50 mm Hg, pulse is 102/min, and respirations are 24/min. Examination shows right flank tenderness. The patient subsequently undergoes nephrectomy, and a cut section of the resected kidney is shown in the image below.



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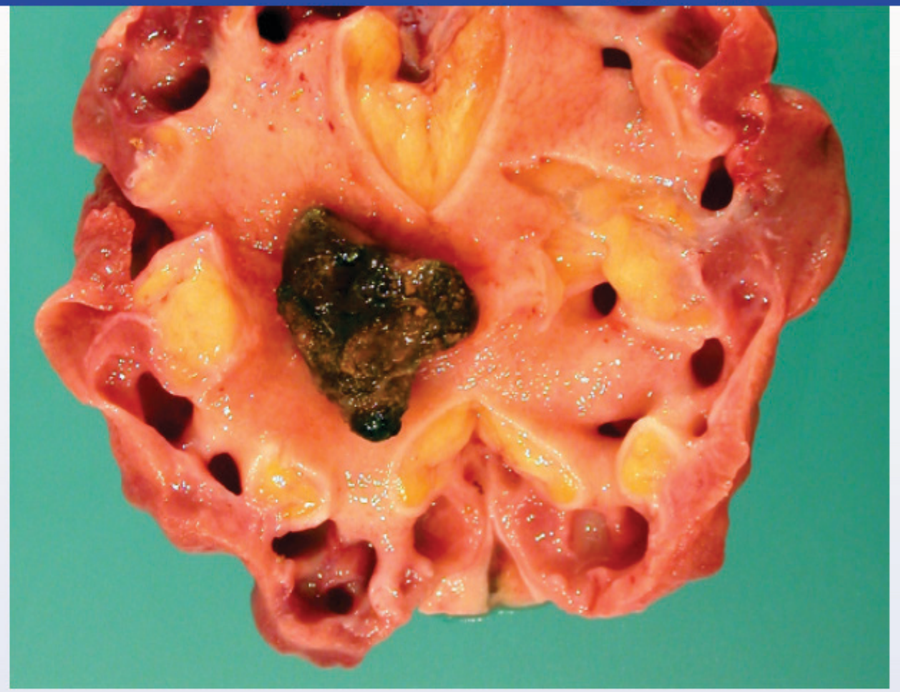
A 54-year-old woman is brought to the hospital due to fever, nausea, vomiting, and confusion. For the past 2 days
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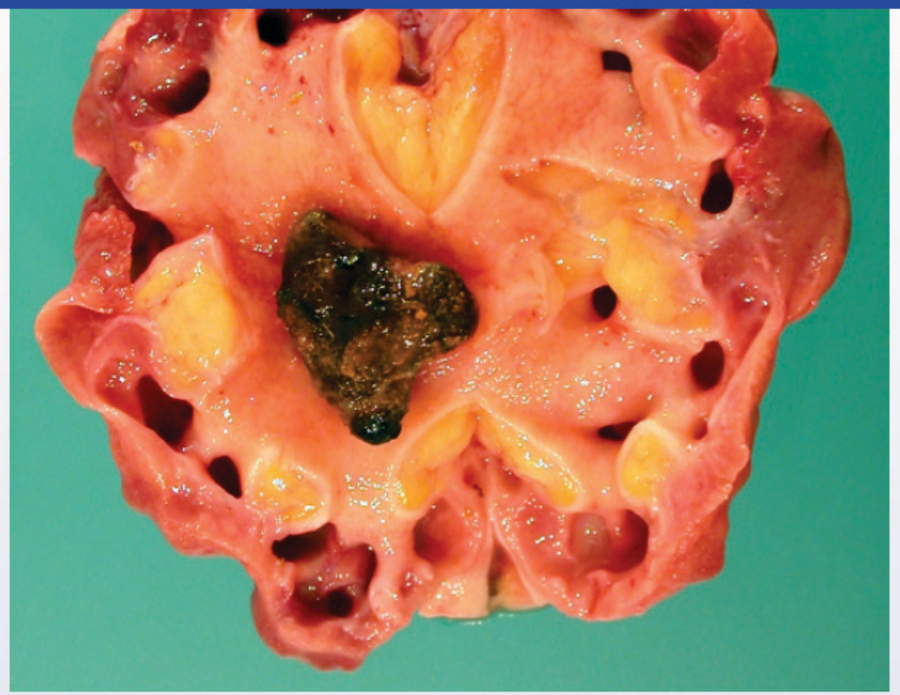


Further evaluation of this patient would most likely reveal which of the following?

- A. *Escherichia coli* infection
- B. High urinary cystine excretion
- C. *Klebsiella* infection
- D. Parathyroid tumor
- E. Persistently low urine pH

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Further evaluation of this patient would most likely reveal which of the following?

- A. *Escherichia coli* infection (16%)
- ✗ B. High urinary cystine excretion (14%)
- ✓ C. *Klebsiella* infection (49%)
- D. Parathyroid tumor (4%)
- E. Persistently low urine pH (14%)

Incorrect
Correct answer
C

49%
Answered correctly

15 secs
Time Spent

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Struvite (magnesium ammonium phosphate) stones	
Risk factors	• Recurrent upper urinary tract infection • Urease-producing organisms (eg, *Klebsiella*, *Proteus*)
Pathogenesis	• Hydrolysis of urea to yield ammonia: $\text{Urea} \rightarrow 2\ NH_3 + CO_2$ $NH_3 + H_2O \rightarrow NH_4^+ + OH^-$ • Increased urine pH • Precipitation of magnesium ammonium phosphate salts
Clinical features	• Large staghorn calculi • Fever, mild flank pain due to infection • Obstruction of collecting system & atrophy of renal parenchyma

This patient has a large staghorn calculus in the renal pelvis associated with dilation of the collecting system and atrophy of the renal cortex. **Staghorn calculi** are composed primarily of **struvite** (magnesium ammonium phosphate) and calcium salts (carbonate, oxalate, or phosphate). They are typically seen in patients with recurrent upper urinary infection caused by **urease-producing organisms** (eg, *Proteus*, *Klebsiella*); hydrolysis of urea yields **ammonia**, which **alkalinizes the urine** (pH usually >7) and facilitates precipitation of magnesium ammonium phosphate crystals **(Choice E)**.

Because of the large quantities of urea excreted in urine, these stones can grow very rapidly and fill the renal calyces, causing **obstruction** of renal outflow. The kidneys are often **atrophic** due to recurrent infection and/or chronic obstructive nephropathy. The large size of staghorn calculi prevents them from passing into the ureter, so symptoms are typically related to the associated infection (eg, fever, mild costovertebral pain, hematuria) rather than acute renal colic.

(Choice A) *Escherichia coli* is the most common cause of uncomplicated urinary tract infections but only rarely

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phosphate) and calcium salts (carbonate, oxalate, or phosphate). They are typically seen in patients with recurrent upper urinary infection caused by **urease-producing organisms** (eg, *Proteus*, *Klebsiella*); hydrolysis of urea yields **ammonia**, which **alkalinizes the urine** (pH usually >7) and facilitates precipitation of magnesium ammonium phosphate crystals **(Choice E)**.

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(Choice A) *Escherichia coli* is the most common cause of uncomplicated urinary tract infections but only rarely produces urease. It is not commonly associated with the formation of staghorn calculi.

(Choice B) Cystine stones are uncommon, yellow-brown calculi that precipitate in acidic urine. They usually develop in patients who have cystinuria secondary to genetic defects impairing renal cystine reabsorption. Although cystinuria can sometimes result in large staghorn calculi due to persistent cystine excretion, this patient's recurrent urinary tract infections are more suggestive of struvite stone formation.

(Choice D) Hyperparathyroidism due to a parathyroid adenoma can cause increased serum calcium levels that ultimately result in increased urinary calcium filtration, predisposing to formation of calcium oxalate stones. These stones typically present with renal colic due to acute ureterolithiasis, and most patients do not have significant fever or a history of recurrent urinary tract infection.

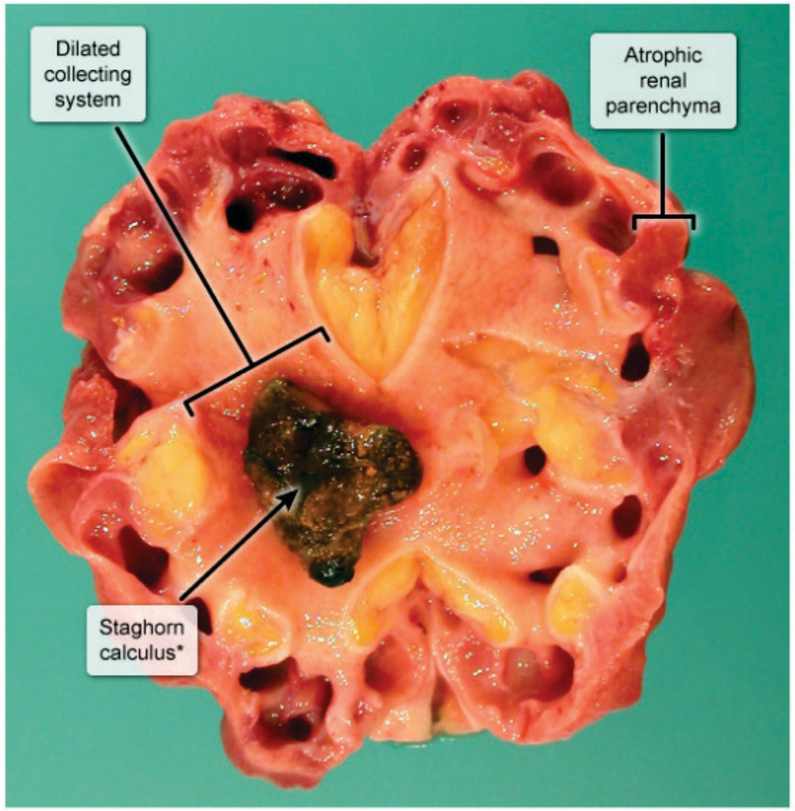
Educational objective:
Staghorn calculi are large renal stones that take on the shape of the renal calyces. They are composed primarily of struvite (magnesium ammonium phosphate) and are associated with recurrent upper urinary tract infections by urease-producing organisms (eg, *Proteus*, *Klebsiella*). Hydrolysis of urea yields ammonia, which alkalinizes the urine and facilitates precipitation of struvite crystals.

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Pathogenesis	$NH_3 + H_2O \rightarrow NH_4^+ + OH^-$ • Increased urine pH

Exhibit Display

Staghorn calculus



*Composed of magnesium ammonium phosphate (struvite).

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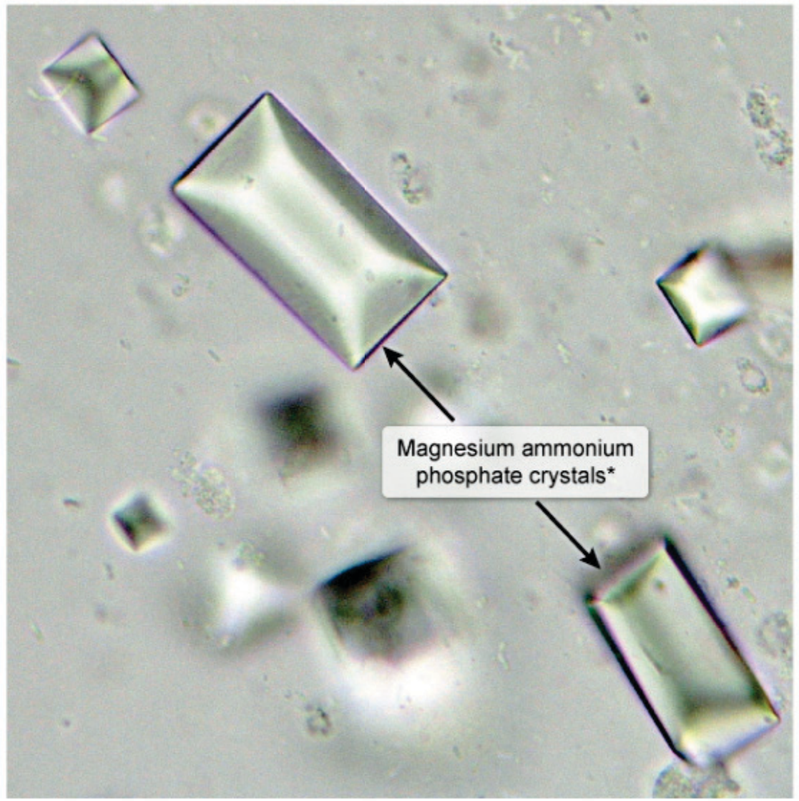
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Pathogenesis	$NH_3 + H_2O \rightarrow NH_4^+ + OH^-$ • Increased urine pH

Exhibit Display

Magnesium ammonium phosphate crystals



*"Coffin lid" crystals precipitate in alkaline urine.

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(Choice D) Hyperparathyroidism due to a parathyroid adenoma can cause increased serum calcium levels that

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A 68-year-old man comes to the emergency department due to a 1-week history of increasing leg and abdominal swelling. The patient has a history of pulmonary hypertension and cor pulmonale from advanced chronic obstructive pulmonary disease. Other medical conditions include hypertension and gout. Physical examination shows scattered rhonchi, prolonged expiratory phase of expiration, mild ascites, and extensive edema of the abdominal wall and lower extremities. The patient is hospitalized and intravenous loop diuretic therapy is begun. Two days later, acetazolamide is added to his treatment regimen. Which of the following most likely prompted the additional therapy in this patient?

- A. Hyperuricemia
- B. Hypokalemia
- C. Inadequate diuresis
- D. Metabolic alkalosis
- E. Prerenal azotemia

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- A. Hyperuricemia (8%)
- ✗ B. Hypokalemia (12%)
- C. Inadequate diuresis (11%)
- ✓ D. Metabolic alkalosis (65%)
- E. Prerenal azotemia (2%)

Incorrect
Correct answer
D

65%
Answered correctly

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Time Spent

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Explanation

Diuretic effects on total body electrolyte levels

Diuretic type	Na^+	K^+	HCO_3^-	Ca^{2+}	Uric acid

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Diuretic effects on total body electrolyte levels					
Diuretic type	**Na^+**	**K^+**	**HCO_3^-**	**Ca^{2+}**	**Uric acid**
Loop (eg, furosemide)	↓↓↓	↓↓	↑↑	↓	↑
Thiazide (eg, HCTZ, metolazone)	↓↓	↓	↑	↑	↑
Potassium sparing (eg, spironolactone, amiloride)	↓	↑	↓	—	—
Carbonic anhydrase inhibitor (eg, acetazolamide)	↓	↓	↓	↓	—
HCTZ = hydrochlorothiazide.					

Loop diuretics (eg, furosemide) inhibit the Na^+-K^+-$2Cl^-$ transporter in the ascending loop of Henle to stimulate potent excretion of Na^+ and water and reduce total body fluid volume. Electrolyte abnormalities are common with the use of loop diuretics; **metabolic alkalosis** occurs due to the following mechanisms:

- Sodium and water losses induced by diuretic therapy (ie, volume contraction) cause increased aldosterone-mediated **renal excretion of H^+** and K^+.
- Loop diuretics cause relatively greater loss of Cl^- than Na^+, resulting in decreased total body electronegativity. In response, the **kidneys retain more HCO_3^-**, the second most abundant anion in the body, to maintain electrochemical balance.

This metabolic alkalosis can have important implications because it stimulates compensatory hyperventilation that

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This metabolic alkalosis can have important implications because it stimulates compensatory hypoventilation that may hinder weaning from mechanical ventilation in critically ill patients. **Carbonic anhydrase inhibitors** (eg, acetazolamide) help **offset the metabolic alkalosis**; these drugs inhibit the reabsorption of sodium bicarbonate ($NaHCO_3$) in the proximal tubule, leading to increased HCO_3^- excretion. The metabolic acidosis that is generated reduces blood alkalinity to help normalize pH.

(Choice A) Loop diuretics increase renal uric acid reabsorption, reducing uric acid excretion and facilitating hyperuricemia, thereby increasing risk of gout. Probenecid blocks proximal tubule uric acid reabsorption and may reduce loop diuretic–associated hyperuricemia.

(Choice B) Potassium-sparing diuretics (eg, spironolactone) can help offset the hypokalemia caused by loop diuretics by reducing K^+ secretion in the collecting tubules. Potassium-sparing diuretics also encourage a mild metabolic acidosis, but less so than carbonic anhydrase inhibitors.

(Choice C) Carbonic anhydrase inhibitors have only a weak diuretic effect because most of the Na^+ blocked from reabsorption in the proximal tubules is reabsorbed in the loop of Henle and distal tubule. In contrast, thiazide diuretics, when used in combination with loop diuretics, block reabsorption of the increased Na^+ load delivered to the distal convoluted tubules, producing a profound synergistic diuresis.

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(Choice E) Loop diuretics cause significant intravascular volume depletion with reduced renal perfusion and consequent renal retention of urea (evidenced by blood urea nitrogen/creatinine ratio >20). This prerenal azotemia is improved by temporary diuretic cessation to allow intravascular volume to reaccumulate, but it is not improved by carbonic anhydrase inhibitor therapy.

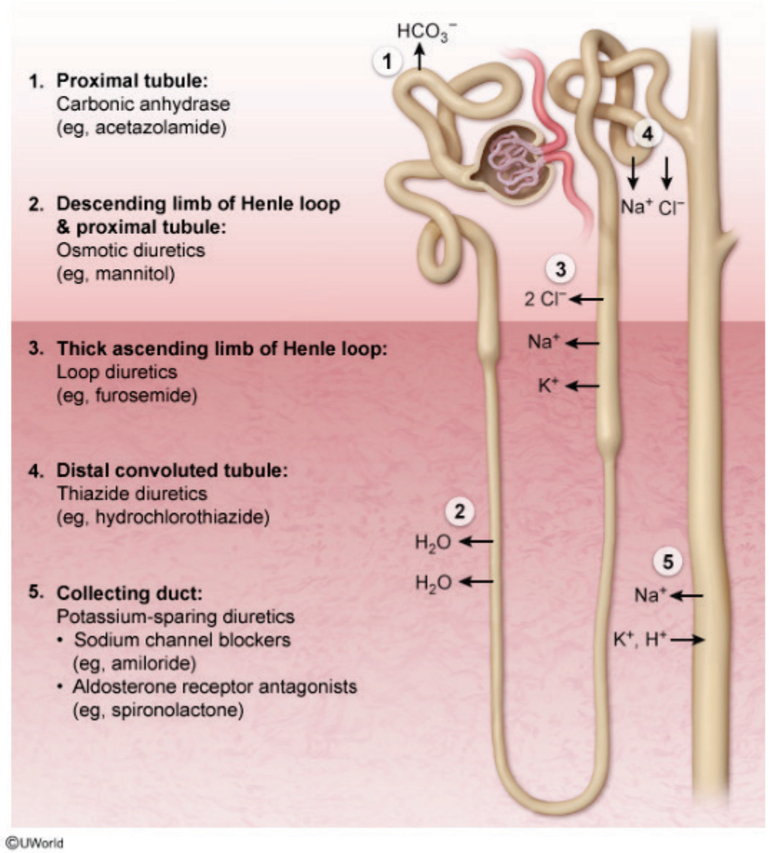
Educational objective:
Carbonic anhydrase inhibitors (eg, acetazolamide) block the reabsorption of sodium bicarbonate in the proximal tubule to cause metabolic acidosis. These drugs can be used to help offset the metabolic alkalosis caused by loop diuretics.

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Potassium sparing	↓	↑	↓	—	—

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Site of action for various diuretics



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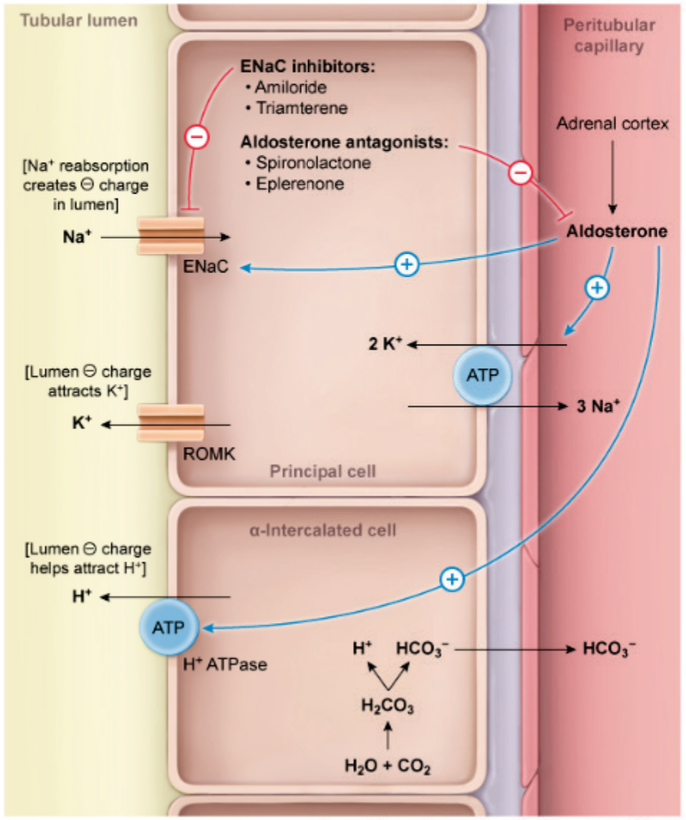
(Choice B) Potassium-sparing diuretics (eg, spironolactone) can help offset the hypokalemia caused by loop diuretics by reducing K^+ secretion in the collecting tubules. Potassium-sparing diuretics also encourage a mild

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Potassium sparing	↓	↑	↓	—	—

Exhibit Display

Action of aldosterone in the collecting duct of the nephron



ENaC = epithelial sodium channel; **ROMK** = renal outer medullary potassium channel. ©UWorld

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A 20-year-old woman comes to the office due to intermittent pain and swelling of both knees over the past 3 months. She has no fever, chills, or abnormal vaginal discharge. The patient has no other medical conditions and is not sexually active. Temperature is 37.2 C (99 F), blood pressure is 150/90 mm Hg, and pulse is 78/min. Small, nontender oral ulcers are present. Examination shows mild tenderness of the knee joints but no effusion. The remainder of the examination shows no abnormalities. Laboratory results reveal anemia, thrombocytopenia, and elevated serum creatinine. Urinalysis shows proteinuria and red blood cell casts. Which of the following pathogenic mechanisms is most likely responsible for this patient's renal disease?

- A. Activation of $CD8^+$ T lymphocytes
- B. Deposition of immune complexes containing bacterial antigens
- C. Deposition of immune complexes containing DNA and anti-DNA
- D. Deposition of immunoglobulin light chains
- E. Formation of autoantibodies to podocyte antigens

Submit

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A 20-year-old woman comes to the office due to intermittent pain and swelling of both knees over the past 3 months. She has no fever, chills, or abnormal vaginal discharge. The patient has no other medical conditions and is not sexually active. Temperature is 37.2 C (99 F), blood pressure is 150/90 mm Hg, and pulse is 78/min. Small, nontender oral ulcers are present. Examination shows mild tenderness of the knee joints but no effusion. The remainder of the examination shows no abnormalities. Laboratory results reveal anemia, thrombocytopenia, and elevated serum creatinine. Urinalysis shows proteinuria and red blood cell casts. Which of the following pathogenic mechanisms is most likely responsible for this patient's renal disease?

- A. Activation of $CD8^+$ T lymphocytes (3%)
- ✗ B. Deposition of immune complexes containing bacterial antigens (9%)
- ✓ C. Deposition of immune complexes containing DNA and anti-DNA (73%)
- D. Deposition of immunoglobulin light chains (7%)
- E. Formation of autoantibodies to podocyte antigens (5%)

Incorrect
Correct answer
C

73%
Answered correctly

17 secs
Time Spent

2023
Version

Explanation

This young woman with hypertension, elevated serum creatinine, proteinuria, and red blood cells casts on urinalysis has **glomerulonephritis**. In association with the transient arthralgias, oral ulcers, and cytopenia, this presentation suggests systemic lupus erythematosus (SLE) complicated by **lupus nephritis**. SLE is an autoimmune disease that occurs due to the formation of autoantibodies against cell surface and nuclear antigens. Disease manifestations result from direct tissue injury by the autoantibodies or from the formation of circulating

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This young woman with hypertension, elevated serum creatinine, proteinuria, and red blood cells casts on urinalysis has **glomerulonephritis**. In association with the transient arthralgias, oral ulcers, and cytopenia, this presentation suggests systemic lupus erythematosus (SLE) complicated by **lupus nephritis**. SLE is an autoimmune disease that occurs due to the formation of autoantibodies against cell surface and nuclear antigens. Disease manifestations result from direct tissue injury by the autoantibodies or from the formation of circulating immune complexes that deposit in tissues.

Lupus nephritis occurs primarily due to deposition of **DNA/anti-DNA immune complexes** within the glomerulus (eg, mesangium, subendothelial or subepithelial space). This results in the activation of complement and the recruitment of inflammatory cells **(type III hypersensitivity)**, leading to glomerular injury and reduced renal function. Elevated levels of anti-DNA antibodies often precede clinically apparent renal disease and can be used to monitor disease activity.

(Choice A) Activation of $CD4^+$ and $CD8^+$ T lymphocytes by donor histocompatibility antigens occurs during acute cellular rejection of a renal allograft. CD8+ T cells do not play a prominent role in the pathogenesis of lupus nephritis.

(Choice B) Poststreptococcal glomerulonephritis is another cause of nephritic syndrome and results from glomerular deposition of immune complexes involving streptococcal antigens. However, it typically occurs 1-4 weeks after an infection (eg, impetigo, pharyngitis) and is far more common in young children. In addition, it is not associated with oral ulcers or cytopenias.

(Choice D) Multiple myeloma can cause anemia and bone pain; kidney injury occurs due to monoclonal free light-chain deposition in the renal tubules. However, urinalysis would be expected to demonstrate waxy casts composed of Bence Jones proteins, not red blood cell casts. In addition, multiple myeloma does not cause oral ulcers and is extremely uncommon in young patients.

(Choice E) Autoantibodies against podocyte antigens occurs in membranous nephropathy. Although membranous nephropathy can occur in SLE, it results in nephrotic syndrome characterized by massive proteinuria

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(Choice E) Autoantibodies against podocyte antigens occurs in membranous nephropathy. Although membranous nephropathy can occur in SLE, it results in nephrotic syndrome characterized by massive proteinuria and edema. Red blood cell casts are unexpected.

Educational objective:
Systemic lupus erythematosus is an autoimmune disease characterized by the formation of antinuclear antibodies (eg, anti-DNA antibodies). Lupus nephritis occurs primarily due to the formation of immune complexes containing DNA and anti-DNA in the circulation. These are deposited in the glomerulus where they result in complement activation, recruitment of inflammatory cells, and renal injury (type III hypersensitivity).

References

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Explanation

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ulcers and is extremely uncommon in young patients.

Exhibit Display

Manifestations of systemic lupus erythematosus	
Clinical symptoms	• Constitutional: fever, fatigue & weight loss • Symmetric, migratory arthritis • Skin: butterfly rash & photosensitivity • Serositis: pleurisy, pericarditis & peritonitis • Thromboembolic events (due to vasculitis & antiphospholipid antibodies) • Neurologic: cognitive dysfunction & seizures
Laboratory findings	• Hemolytic anemia, thrombocytopenia & leukopenia • Hypocomplementemia (C3 & C4) • Antibodies: ◦ Antinuclear antibodies (sensitive) ◦ Anti-dsDNA & anti-Smith (specific) • Renal involvement: proteinuria & elevated creatinine
dsDNA = double-stranded DNA.	

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A 64-year-old man comes to the office due to generalized edema, fatigue, and dyspnea on exertion for 2 months. The patient has a 25-year history of poorly controlled rheumatoid arthritis. Temperature is 36.9 C (98.4 F), blood pressure is 108/70 mm Hg, and pulse is 90/min. The patient is thin and appears chronically ill but is in no acute distress. There is no lymphadenopathy. Breath sounds are decreased at the lung bases. Musculoskeletal examination shows severe deformities of the hands and feet related to rheumatoid arthritis. There is pitting edema of both legs up to the knees. Peripheral pulses are normal. Urinalysis shows 4+ protein but is otherwise normal. A renal biopsy is performed. Which of the following histologic abnormalities is most likely to be seen in this patient's glomeruli?

- A. Crescent formation
- B. Deposition of amorphous material
- C. Diffuse hypercellularity
- D. IgA deposition
- E. No abnormalities

Submit

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- A. Crescent formation (16%)
- ✓ B. Deposition of amorphous material (47%)
- C. Diffuse hypercellularity (20%)
- D. IgA deposition (7%)
- E. No abnormalities (8%)

Correct

47%
Answered correctly

06 secs
Time Spent

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Explanation

This patient with peripheral edema and heavy proteinuria has **nephrotic syndrome**. Given his long-standing inflammation from poorly controlled **rheumatoid arthritis** (RA), the cause of his nephrotic syndrome is likely **AA amyloidosis**.

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This patient with peripheral edema and heavy proteinuria has **nephrotic syndrome**. Given his long-standing inflammation from poorly controlled **rheumatoid arthritis** (RA), the cause of his nephrotic syndrome is likely **AA amyloidosis**.

Amyloidosis pathogenesis involves excessive misfolding of native protein (eg, light chains, beta2-microglobulin, transthyretin) due to predisposing mutations or excessive protein production. This structural change in soluble precursors promotes formation of beta-pleated sheets that **polymerize** into **insoluble fibrils** and deposit in tissues causing organ dysfunction. Amyloid deposits appear as **amorphous pink material** on light microscopy with apple-green birefringence on Congo red stain under polarized light.

Serum amyloid A, an acute phase reactant induced by cytokines, is excessively produced during **chronic inflammatory states**, resulting in AA amyloidosis. RA is the most common cause, but inflammatory bowel disease, chronic infection (eg, osteomyelitis, tuberculosis), and familial Mediterranean fever are also frequently associated. AA amyloidosis most commonly affects the kidneys, presenting as nephrotic syndrome. Hepatomegaly is frequent with splenomegaly occasionally seen. Cardiac involvement (eg, restrictive cardiomyopathy) is rare.

(Choice A) Crescent formation in glomeruli occur with rapidly progressive glomerulonephritis, which can present with several conditions (eg, anti–glomerular basement membrane antibody disease). However, it rarely occurs in RA and typically presents with an active urine sediment (eg, dysmorphic hematuria, red blood cell casts).

(Choice C) Diffuse hypercellular glomeruli on light microscopy are evident most often with poststreptococcal glomerulonephritis. They are also seen with membranoproliferative glomerulonephritis and lupus nephritis. In addition to proteinuria, these conditions typically have other components of nephritic syndrome (ie, hematuria, hypertension, kidney dysfunction), not nephrotic syndrome.

(Choice D) IgA deposition in the glomerular mesangium is found on immunofluorescence in IgA nephropathy. IgA nephropathy only rarely causes isolated nephrotic syndrome; it typically presents as recurrent, painless hematuria (eg, nephritic syndrome) frequently provoked by upper respiratory tract infection.

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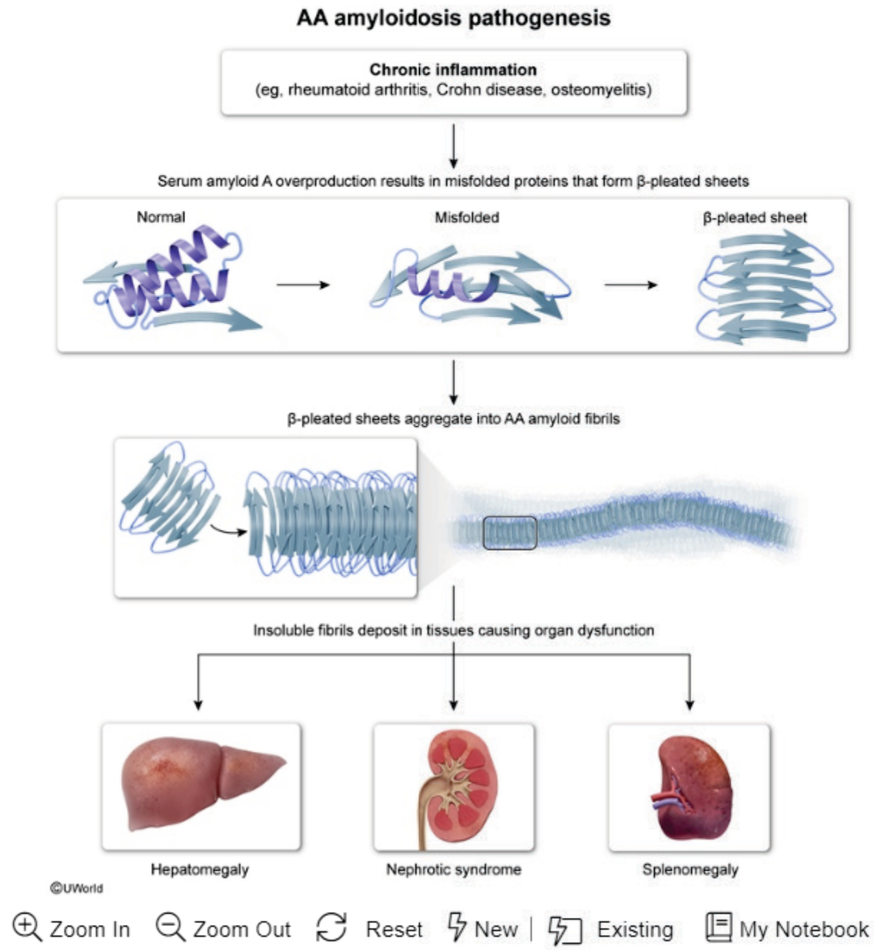
(Choice D) IgA deposition in the glomerular mesangium is found on immunofluorescence in IgA nephropathy. IgA nephropathy only rarely causes isolated nephrotic syndrome; it typically presents as recurrent, painless hematuria (eg, nephritic syndrome) frequently provoked by upper respiratory tract infection.

(Choice E) No abnormality on light microscopy in nephrotic syndrome suggests minimal change disease (MCD). The most common cause of nephrotic syndrome in children, adult MCD is sometimes associated with malignancies, drugs, or infections but not amyloidosis.

Educational objective:
AA amyloidosis results from excessive serum amyloid A produced in rheumatoid arthritis and other chronic inflammatory conditions. Renal disease, the most common manifestation, presents as nephrotic syndrome. Light microscopy shows amorphous pink deposits with apple-green birefringence on Congo red stain under polarized light.

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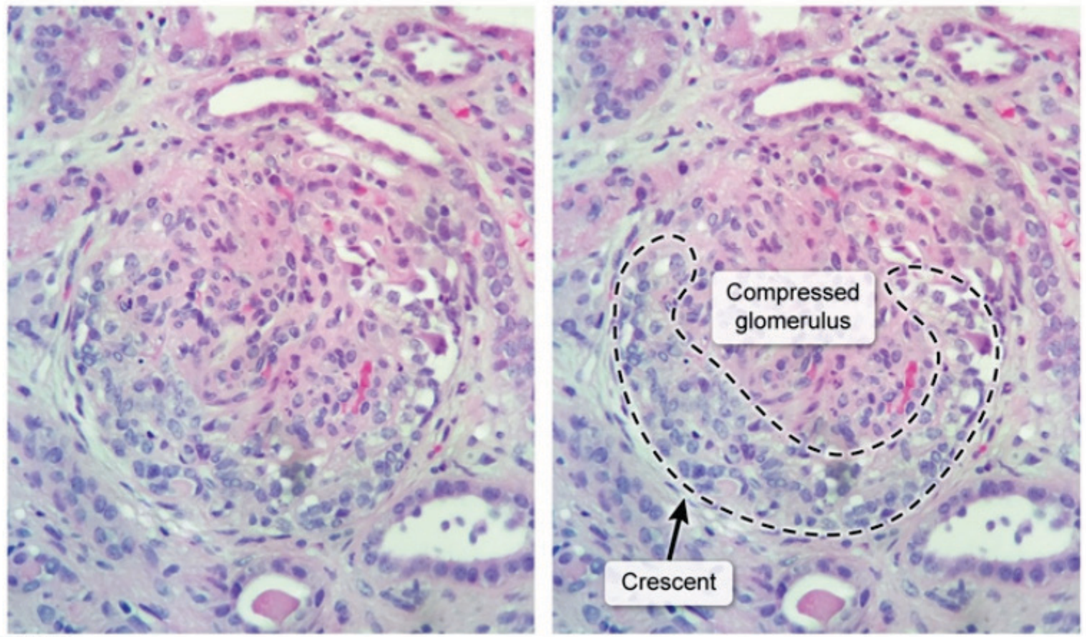
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Crescentic glomerulonephritis



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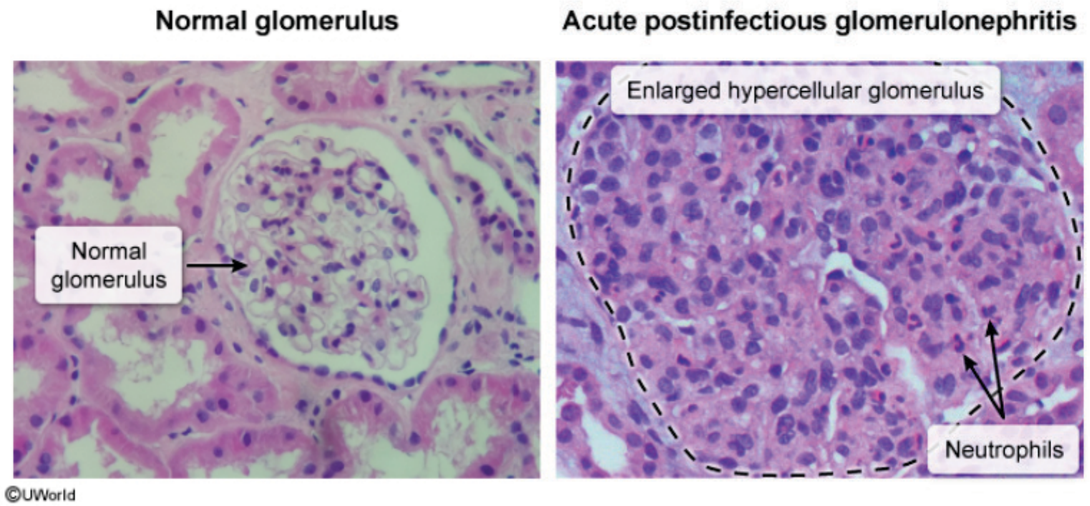
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Acute postinfectious glomerulonephritis | Membranoproliferative glomerulonephritis, Type I



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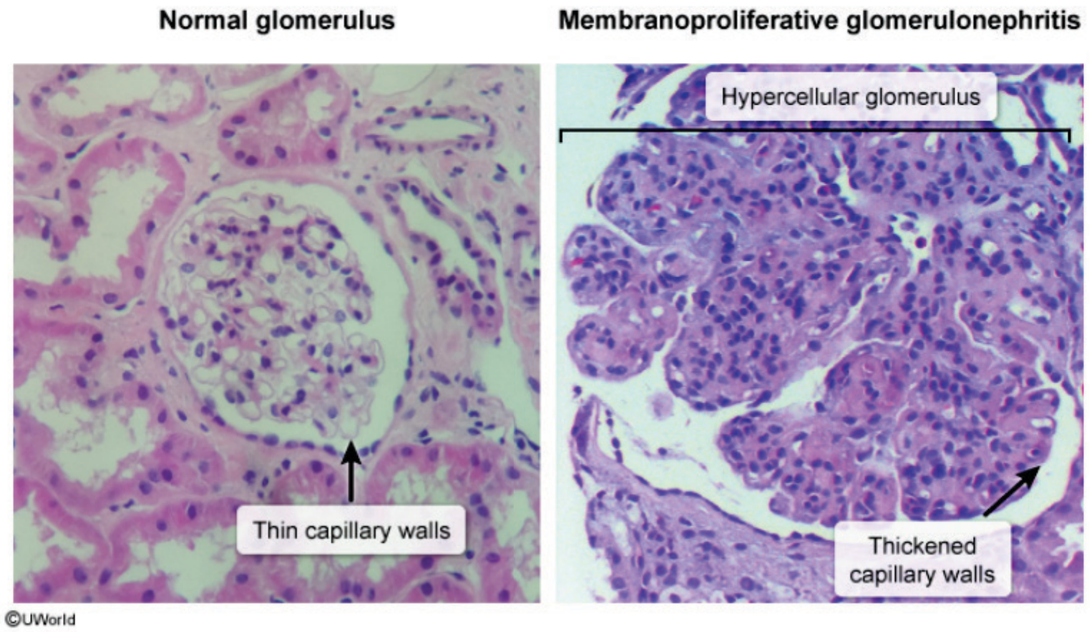
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Acute postinfectious glomerulonephritis | Membranoproliferative glomerulonephritis, Type I

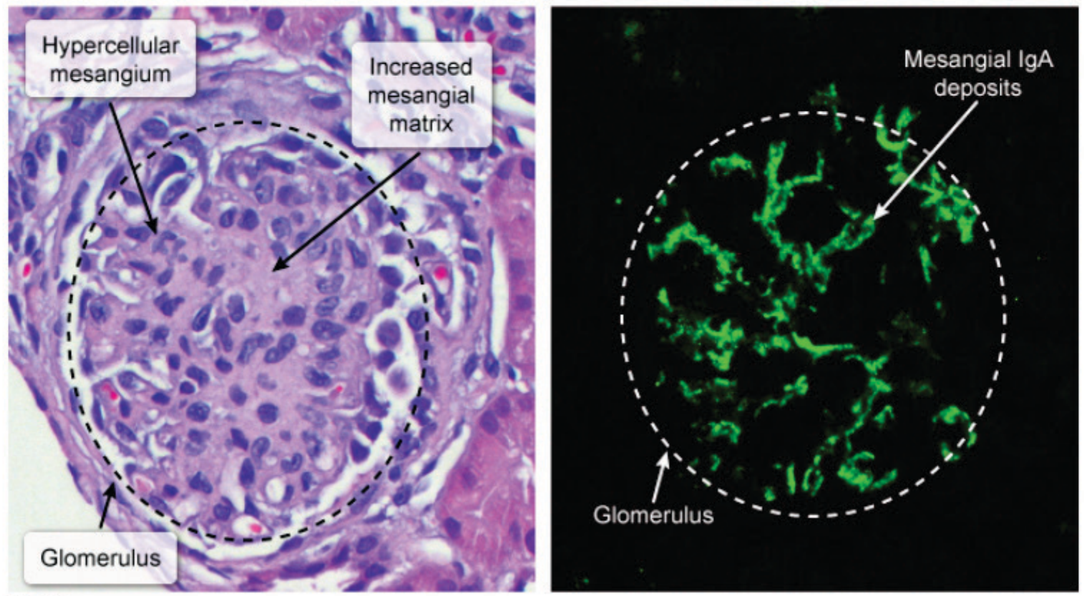


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IgA nephropathy



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The most common cause of nephrotic syndrome in children, adult MCD is sometimes associated with

Serum amyloid A, an acute phase reactant induced by cytokines, is excessively produced during **chronic**

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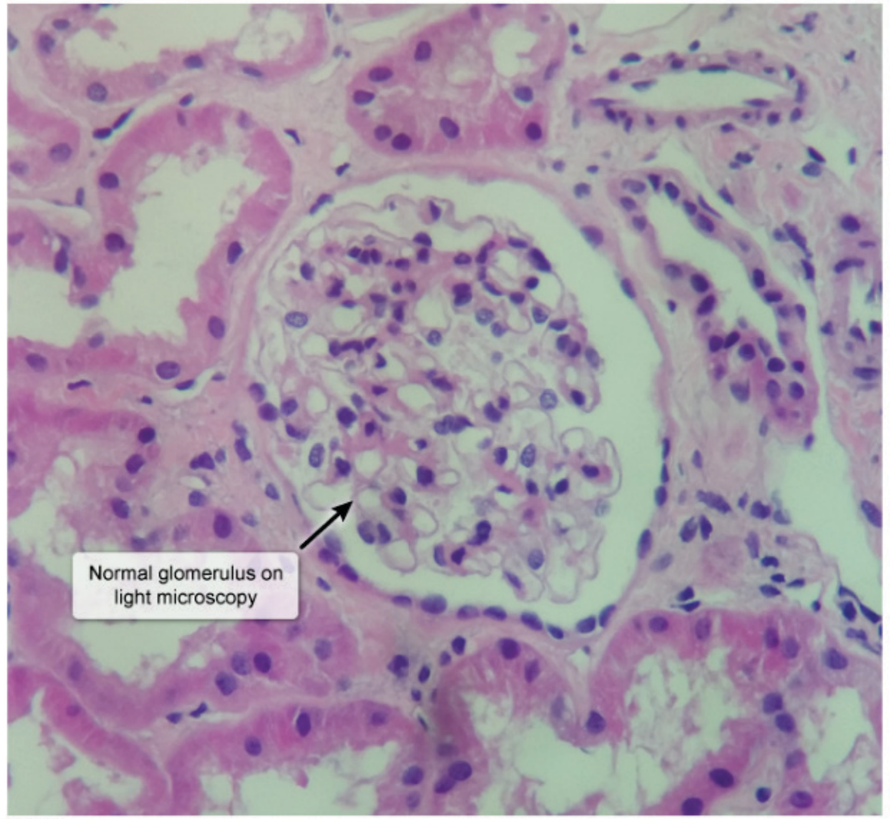
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Minimal change disease



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A 43-year-old man comes to the emergency department due to painful muscle cramps. He also has had a tingling sensation around his mouth since earlier in the day and an intermittent sensation of choking in the throat. The patient reports a history of "high blood pressure and a thyroid disorder." On physical examination, he appears comfortable but anxious. Heart and lung sounds are normal. Light tapping anterior to the ear elicits twitching of the perioral muscles. Further discussion with this patient is most likely to reveal which of the following?

- A. Excessive vitamin D intake
- B. Frequent antacid use
- C. New prescription for chlorthalidone
- D. Nonadherence with levothyroxine
- E. Recent thyroid surgery

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- A. Excessive vitamin D intake (7%)
- ✗ B. Frequent antacid use (4%)
- C. New prescription for chlorthalidone (6%)
- D. Nonadherence with levothyroxine (5%)
- ✓ E. Recent thyroid surgery (75%)

Incorrect
Correct answer
E

75%
Answered correctly

11 secs
Time Spent

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Explanation

Hyperparathyroidism & hypoparathyroidism	
Hyperparathyroidism (↑ PTH)	**Hypoparathyroidism (↓ PTH)**
• ↑ Calcium, ↓ phosphate • Osteoporosis • Nephrolithiasis	• ↓ Calcium, ↑ phosphate • Tingling, numbness • Trousseau & Chvostek signs

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Hyperparathyroidism & hypoparathyroidism	
Hyperparathyroidism (↑ PTH)	**Hypoparathyroidism (↓ PTH)**
• ↑ Calcium, ↓ phosphate • Osteoporosis • Nephrolithiasis • Polydipsia, polyuria • Constipation • Bone pain • Muscle pain	• ↓ Calcium, ↑ phosphate • Tingling, numbness • Trousseau & Chvostek signs • Muscle spasms • Seizures

This patient has symptoms of **hypocalcemia**, including muscle cramps, perioral paresthesias, and possible laryngospasm. Other manifestations of hypocalcemia may include Chvostek sign (facial muscle contraction elicited by tapping on the facial nerve anterior to the ear) and Trousseau sign (carpopedal spasm triggered by prolonged inflation of a blood pressure cuff around the arm). These signs of **neuromuscular hyperexcitability** become clinically apparent with serum calcium levels ≤7.0 mg/dL.

The most common cause of acute hypocalcemia is injury to the **parathyroid glands** during thyroid surgery due to direct trauma, devascularization, or inadvertent removal. Other causes of hypocalcemia include autoimmune hypoparathyroidism, sepsis, tumor lysis syndrome, acute pancreatitis, and severe vitamin D or magnesium deficiency.

(Choices A, B, and C) Excessive intake of vitamin D or calcium-containing antacids can cause hypercalcemia. Thiazide diuretics (eg, chlorthalidone) also can cause mild hypercalcemia due to increased calcium resorption in the distal and collecting tubule of the nephron. Typical presenting symptoms of hypercalcemia include constipation, polyuria/polydipsia, and muscle weakness.

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(Choice D) Hyperthyroidism can cause hypercalcemia due to increased bone turnover. However, in hypothyroid states (eg, due to nonadherence to levothyroxine replacement) circulating calcium is usually normal. In general, hypothyroidism is characterized by chronic fatigue, weight gain, cold intolerance, and diminished reflexes.

Educational objective:
Hypocalcemia can cause muscle cramps, perioral paresthesias, hypotension, and neuromuscular hyperexcitability. Injury to the parathyroid glands during thyroid surgery is a common cause of hypoparathyroidism and acute hypocalcemia.

References

- Clinical and biochemical factors affecting postoperative hypocalcemia after near-total thyroidectomy.

Pathophysiology Renal, Urinary Systems & Electrolytes Hypoparathyroidism

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- Constipation
- Bone pain
- Seizures

Exhibit Display

Signs of hypocalcemia

Trousseau sign
Induction of carpopedal spasm by inflation of a blood pressure cuff above SBP for 3 minutes



Chvostek sign
Contraction of the ipsilateral facial muscles elicited by tapping the facial nerve just anterior to the ear



SBP = systolic blood pressure.

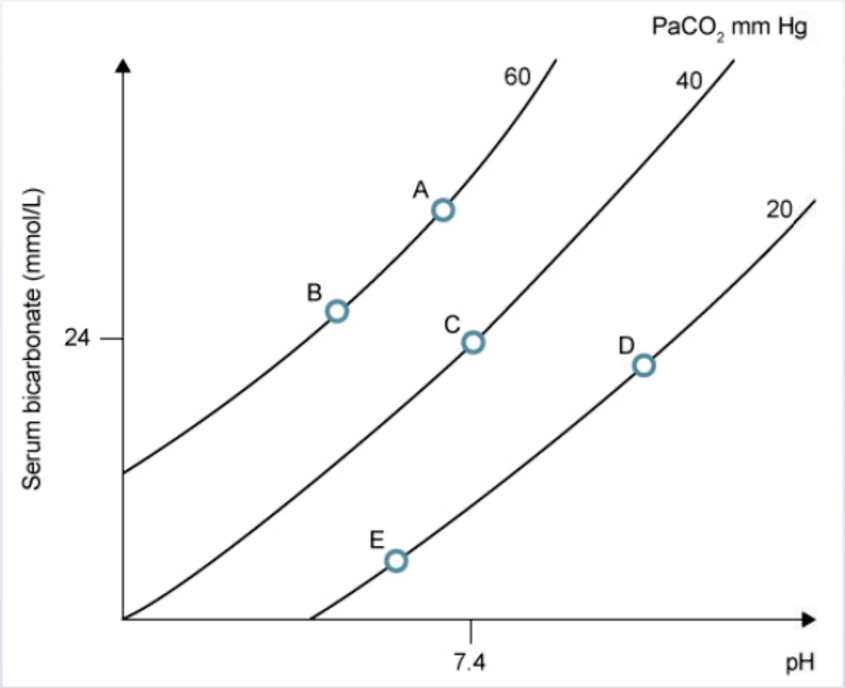
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References

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A 28-year-old man is found unresponsive by his roommate and is brought to the emergency department. He has a history of injection drug use. On physical examination, the patient is obtunded and hypopneic. The pupils are pinpoint. Lung auscultation reveals decreased breath sounds bilaterally. Endotracheal intubation is planned for airway protection and arterial blood gas analysis is performed prior to the procedure while the patient is breathing room air. This patient's current acid-base status is best represented by which of the following points on the below graph?

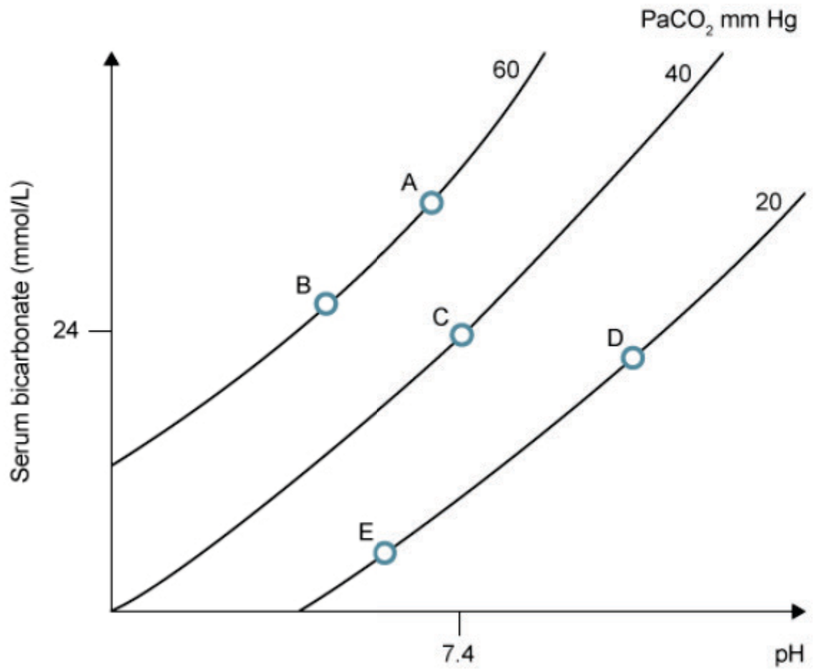


- A. A
- B. B
- C. C

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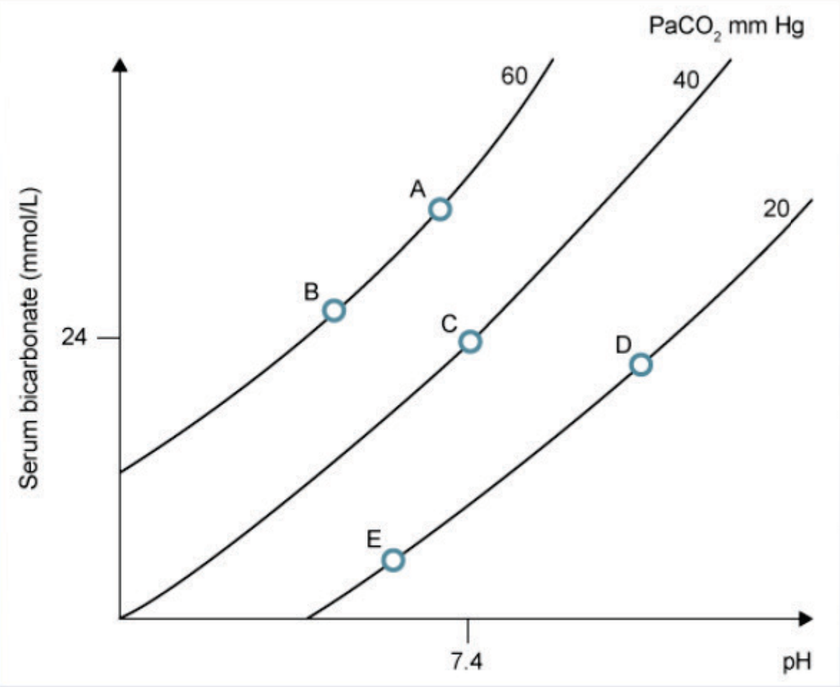
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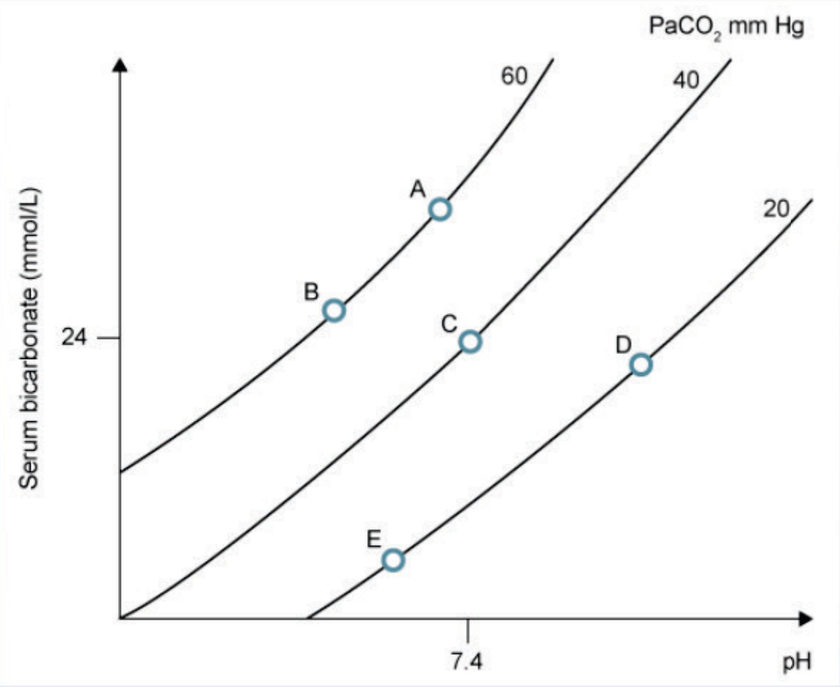
graph?



- A. A
- B. B
- C. C
- D. D
- E. E

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graph?



- A. A (12%)
- ✓ B. B (77%)
- C. C (0%)
- D. D (3%)
- E. E (6%)

Correct

77%
Answered correctly

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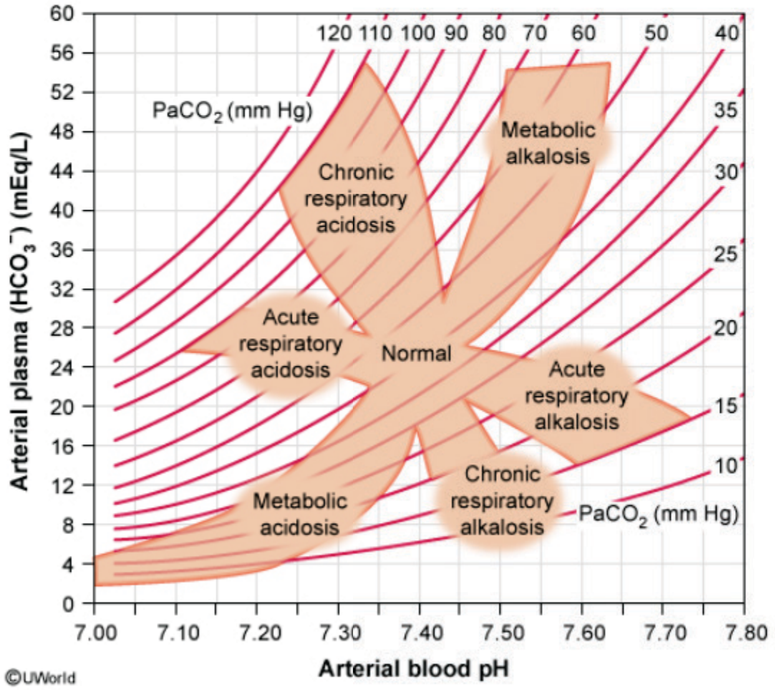
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Answered correctly

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respiratory acidosis, the kidneys retain additional bicarbonate; however, metabolic renal compensation for an acid-

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This patient's altered consciousness, pinpoint pupils, decreased breath sounds, and history of intravenous drug use strongly suggest **acute opioid overdose**. In addition to causing sedation, opioids cause **respiratory depression** by suppressing central respiratory drive in the medulla. The resulting **hypoventilation** leads to CO_2 retention and **acute respiratory acidosis**, characterized by **low pH** and **high $PaCO_2$**. To compensate for respiratory acidosis, the kidneys retain additional bicarbonate; however, metabolic renal compensation for an acid-base disturbance is a relatively slow process (taking place over several days) and is minimally evident in the acute setting.

(Choice A) A high $PaCO_2$ with high serum bicarbonate and near normal pH is consistent with chronic respiratory acidosis with a compensatory metabolic alkalosis, such as occurs in severe chronic obstructive pulmonary disease. Although acute opioid overdose is expected to cause a rapid increase in $PaCO_2$, serum bicarbonate is near normal because there has not been time for metabolic compensation.

(Choice C) Normal acid-base values include pH 7.4, $PaCO_2$ 40 mm Hg, and serum bicarbonate 24 mEq/L. Significant deviation from these values represents an acid-base disturbance.

(Choice D) A high pH with low $PaCO_2$ and slightly low serum bicarbonate is consistent with acute respiratory alkalosis, such as occurs with the hyperventilation seen in acute pulmonary embolism or acute anxiety. Serum bicarbonate is only slightly low because the kidneys have had little time to compensate by increasing bicarbonate excretion.

(Choice E) A low pH with low serum bicarbonate and low $PaCO_2$ is consistent with acute metabolic acidosis, such as occurs with lactic acidosis in sepsis. The lungs quickly compensate for the acidemia with hyperventilation to increase exhalation of CO_2 and help normalize pH. Severe metabolic acidosis can lead to respiratory failure if the lungs are unable to keep up with the need to exhale CO_2.

Educational objective:

Acute opioid overdose is characterized by altered level of consciousness, pinpoint pupils, and central respiratory

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depression by suppressing central respiratory drive in the medulla. The resulting **hypoventilation** leads to CO_2 retention and **acute respiratory acidosis**, characterized by **low pH** and **high $PaCO_2$**. To compensate for respiratory acidosis, the kidneys retain additional bicarbonate; however, metabolic renal compensation for an acid-base disturbance is a relatively slow process (taking place over several days) and is minimally evident in the acute setting.

(Choice A) A high $PaCO_2$ with high serum bicarbonate and near normal pH is consistent with chronic respiratory acidosis with a compensatory metabolic alkalosis, such as occurs in severe chronic obstructive pulmonary disease. Although acute opioid overdose is expected to cause a rapid increase in $PaCO_2$, serum bicarbonate is near normal because there has not been time for metabolic compensation.

(Choice C) Normal acid-base values include pH 7.4, $PaCO_2$ 40 mm Hg, and serum bicarbonate 24 mEq/L. Significant deviation from these values represents an acid-base disturbance.

(Choice D) A high pH with low $PaCO_2$ and slightly low serum bicarbonate is consistent with acute respiratory alkalosis, such as occurs with the hyperventilation seen in acute pulmonary embolism or acute anxiety. Serum bicarbonate is only slightly low because the kidneys have had little time to compensate by increasing bicarbonate excretion.

(Choice E) A low pH with low serum bicarbonate and low $PaCO_2$ is consistent with acute metabolic acidosis, such as occurs with lactic acidosis in sepsis. The lungs quickly compensate for the acidemia with hyperventilation to increase exhalation of CO_2 and help normalize pH. Severe metabolic acidosis can lead to respiratory failure if the lungs are unable to keep up with the need to exhale CO_2.

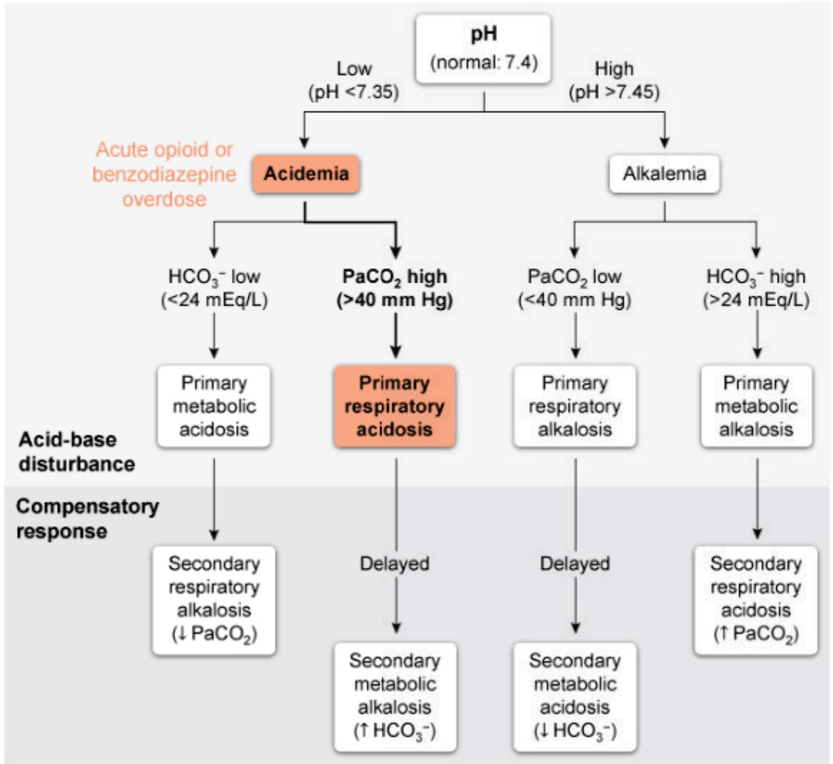
Educational objective:
Acute opioid overdose is characterized by altered level of consciousness, pinpoint pupils, and central respiratory depression. Patients are expected to have acute respiratory acidosis (low pH, high $PaCO_2$) due to hypoventilation. Serum bicarbonate is typically near normal as there is not time for metabolic compensation in the acute setting.

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Exhibit Display

Arterial blood gas interpretation of acid-base disorders



* The normal ranges for $PaCO_2$ and HCO_3^- vary slightly around 40 mm Hg and 24 mEq/L.
For simplicity, these numbers should be used as a normal baseline for acid-base calculations.

HCO_3^- = bicarbonate; **$PaCO_2$** = partial pressure of carbon dioxide in arterial blood.

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A 64-year-old man comes to the office with fatigue. He has hypertension and poorly controlled diabetes complicated by nephropathy and peripheral neuropathy. His renal function has declined steadily over the last few years. On examination, his conjunctivae are pale and he has bilateral 1+ peripheral edema. Laboratory results are as follows:

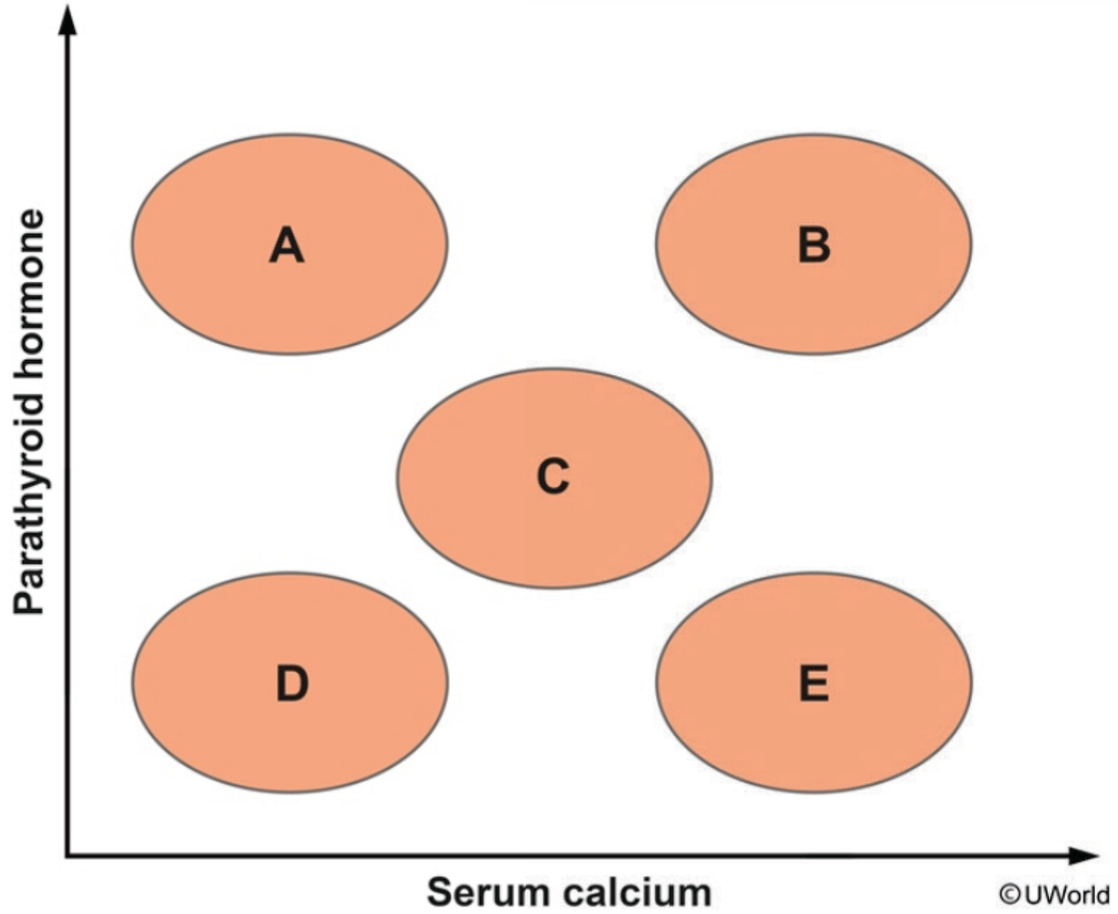
Serum chemistry	
Sodium	133 mEq/L
Potassium	4.4 mEq/L
Chloride	98 mEq/L
Bicarbonate	22 mEq/L
Blood urea nitrogen	76 mg/dL
Creatinine	5.8 mg/dL

On the graph below, area "C" shows the normal relationship between serum concentrations of free calcium and parathyroid hormone. Which of the following areas most likely represents this patient's current metabolic state?

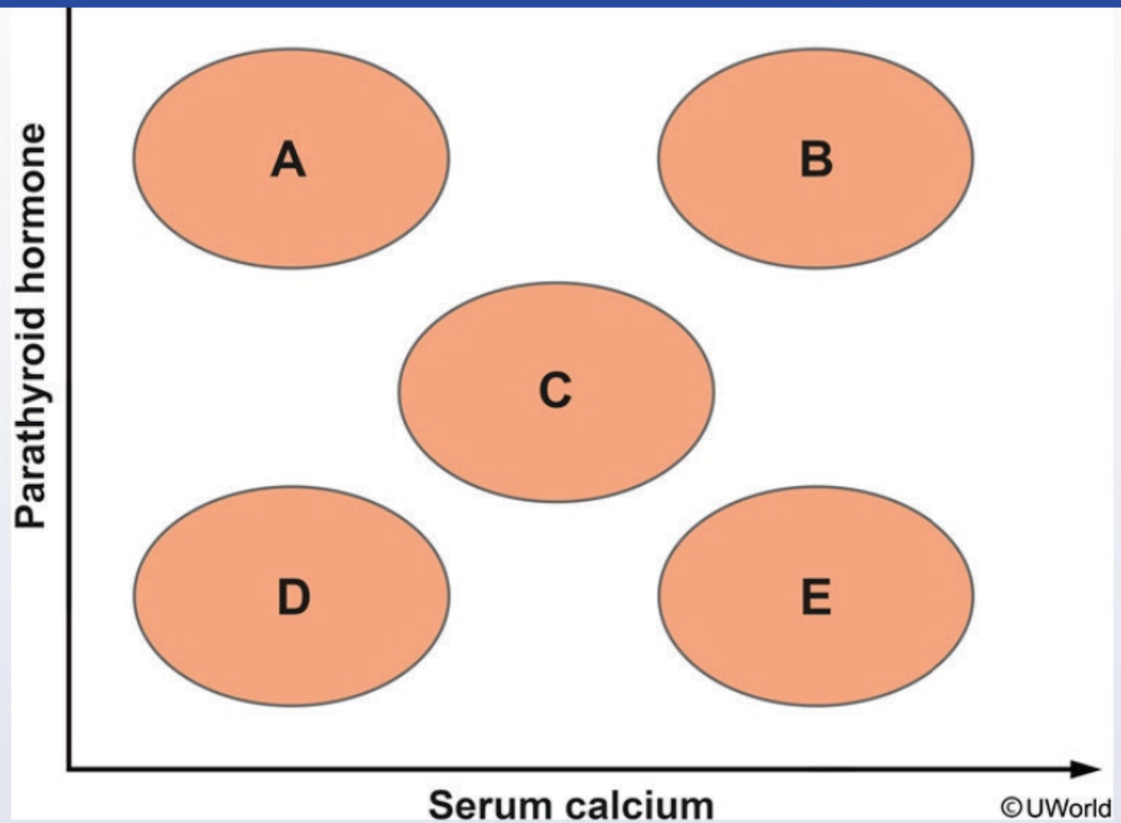
- A. A
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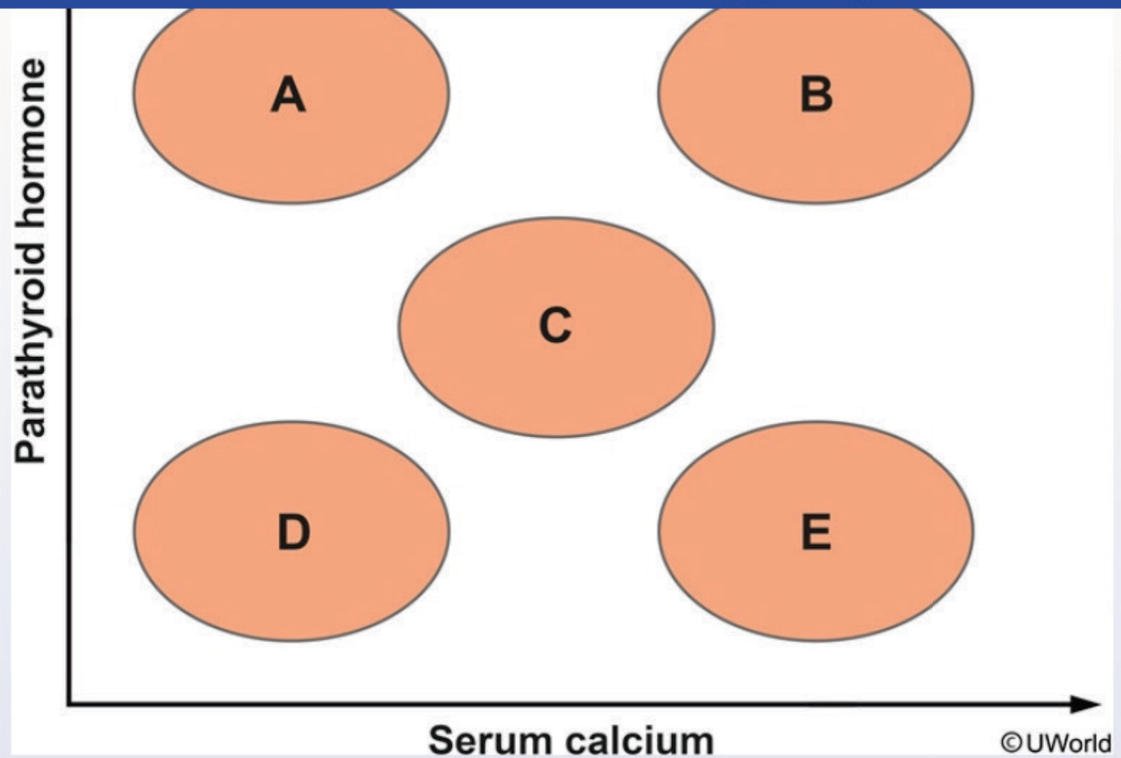
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- A. A
- B. B
- C. C
- D. D
- E. E

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- ✓ A. A (77%)
- B. B (8%)
- ✗ C. C (3%)
- D. D (5%)
- E. E (5%)

Incorrect
Correct answer
A

77%
Answered correctly

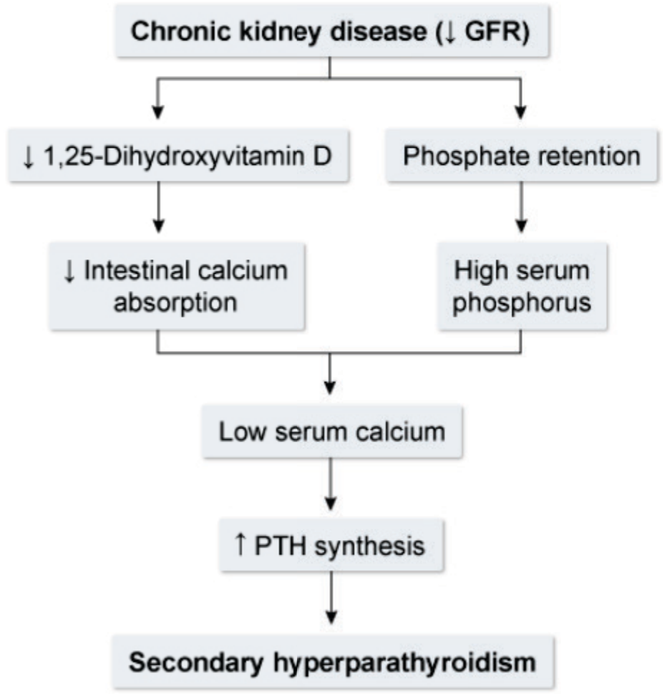
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E. E (5%)

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GFR = glomerular filtration rate; **PTH** = parathyroid hormone.

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In the physiologic state, parathyroid hormone (PTH) causes an overall increase in serum calcium (Ca^{2+}) and a decrease serum phosphate (PO_4) via the following effects:

- Increasing osteoclastic bone resorption, releasing Ca^{2+} and PO_4 into serum
- Increasing renal calcium reabsorption and reducing phosphate reabsorption
- Increasing formation of 1,25-dihydroxycholecalciferol (by upregulating renal 1-alpha-hydroxylase), which increases intestinal Ca^{2+} and PO_4 absorption

PTH production is very sensitive to small changes in serum free Ca^{2+} and is regulated by a negative feedback mechanism: increased Ca^{2+} will suppress PTH, but decreased Ca^{2+} will increase PTH.

In **chronic kidney disease** (CKD), PO_4 clearance declines due to the fall in GFR. The **increased PO_4** binds free serum Ca^{2+}, resulting in **hypocalcemia**. Loss of normal renal parenchyma reduces 1,25-dihydroxyvitamin D synthesis, resulting in a significant decline in intestinal Ca^{2+} absorption and Ca^{2+} release from bone. This further exacerbates the hypocalcemia, which along with hyperphosphatemia and low calcitriol, stimulates PTH production (**secondary hyperparathyroidism**).

(Choice B) In primary hyperparathyroidism, serum Ca^{2+} is elevated but does not suppress PTH due to autonomous gland function. In longstanding CKD, PTH release may become independent of Ca^{2+} levels due to chronic parathyroid cell stimulation; PTH remains elevated despite 1,25-dihydroxyvitamin D and Ca^{2+} supplementation (**tertiary hyperparathyroidism**). However, this is less common than secondary hyperparathyroidism and is usually seen in patients with end-stage renal disease (ie, on dialysis).

(Choice C) Calcitriol and Ca^{2+} supplementation in patients with CKD often returns PTH and Ca^{2+} levels to normal.

(Choice D) Low PTH with hypocalcemia and hyperphosphatemia is seen in hypoparathyroidism.

(Choice E) High serum Ca^{2+} with low PTH is seen in patients with PTH-independent causes of hypercalcemia,

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increases intestinal Ca^{2+} and PO_4 absorption

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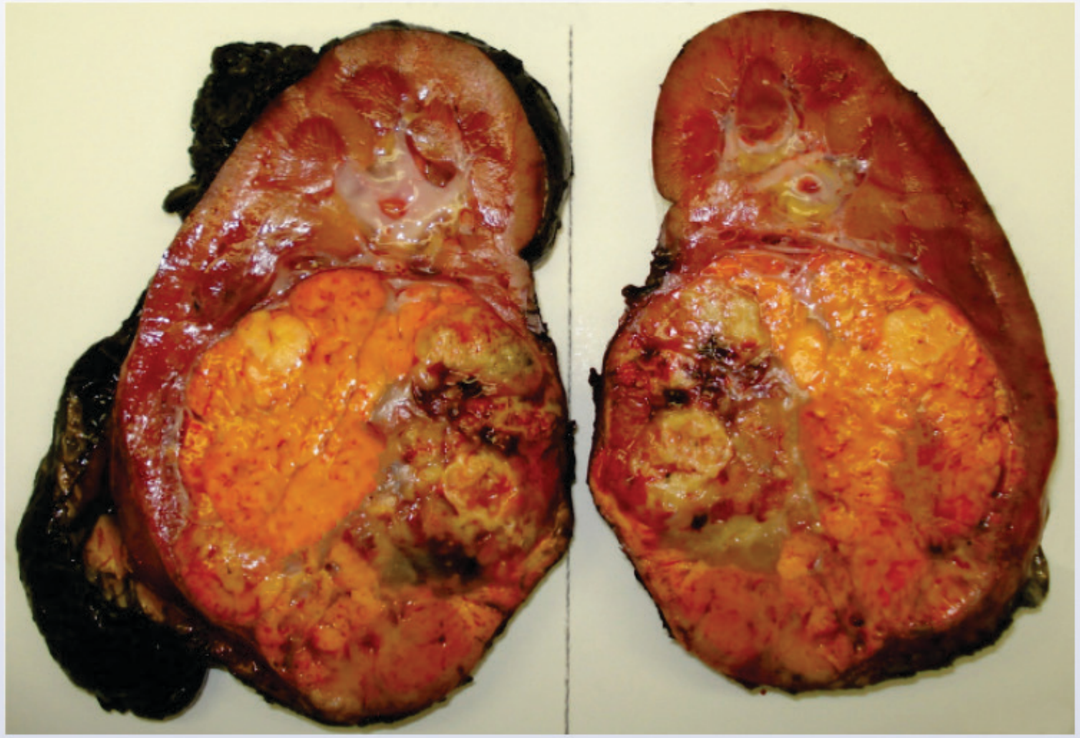
(Choice D) Low PTH with hypocalcemia and hyperphosphatemia is seen in hypoparathyroidism.

(Choice E) High serum Ca^{2+} with low PTH is seen in patients with PTH-independent causes of hypercalcemia, which include hypercalcemia of malignancy, vitamin D toxicity, excessive Ca^{2+} ingestion, thyrotoxicosis, and immobilization (Ca^{2+} resorbed from inactive bones).

Educational objective:
Chronic kidney disease usually causes hyperphosphatemia (binds serum Ca^{2+}) and low 1,25-dihydroxyvitamin D (decreases intestinal Ca^{2+} absorption and Ca^{2+} release from bone). The resulting hypocalcemia stimulates release of parathyroid hormone, causing secondary hyperparathyroidism.

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A 50-year-old man comes to the office for evaluation of abdominal fullness and mild right flank pain. He also reports a weight loss of 4.5 kg (10 lb) over the past 2 months. The patient has no other medical issues and works in a local industrial chemical manufacturing facility. Examination shows a soft abdomen. Ultrasound reveals a mass in the right kidney. A subsequent abdominal CT scan confirms the presence of a large right renal mass with evidence of necrosis. The patient undergoes a right total nephrectomy. The specimen is shown below.



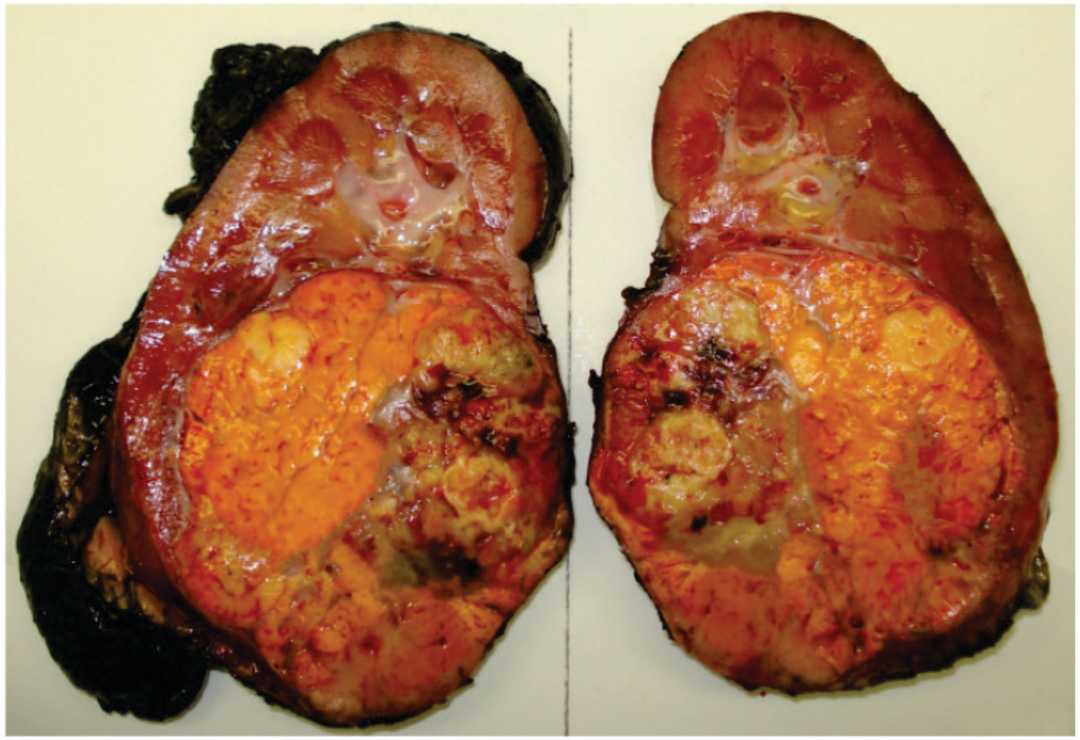
This patient's lesion most likely originated from which of the following portions of the kidney?

- A. Blood vessels
- B. Collecting duct cells

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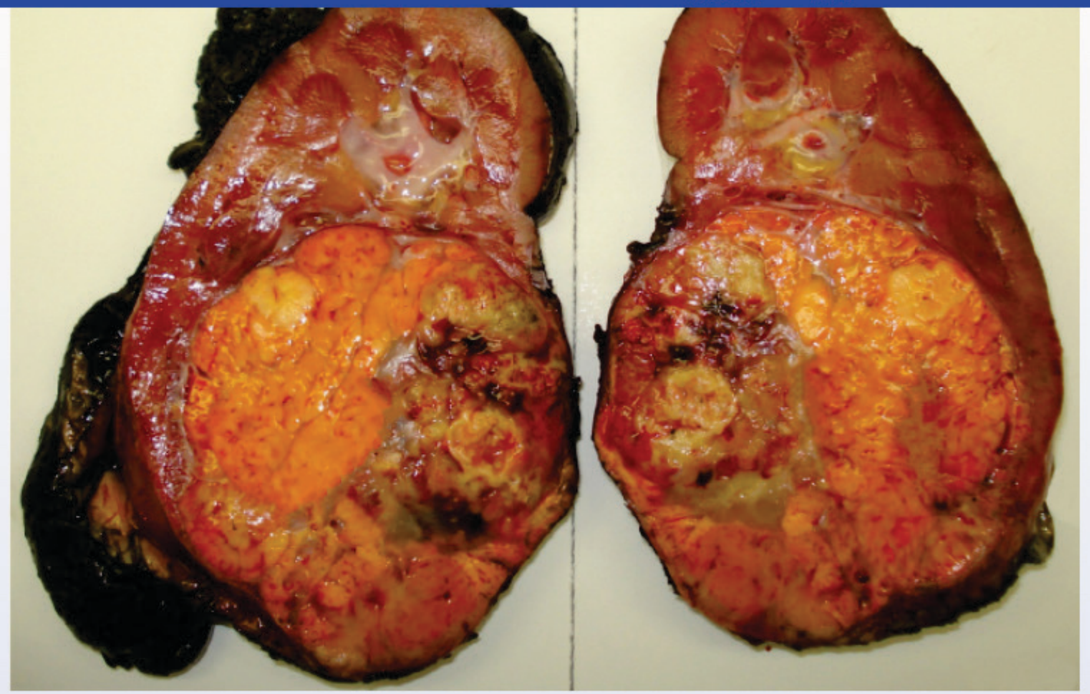


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B. Collecting duct cells

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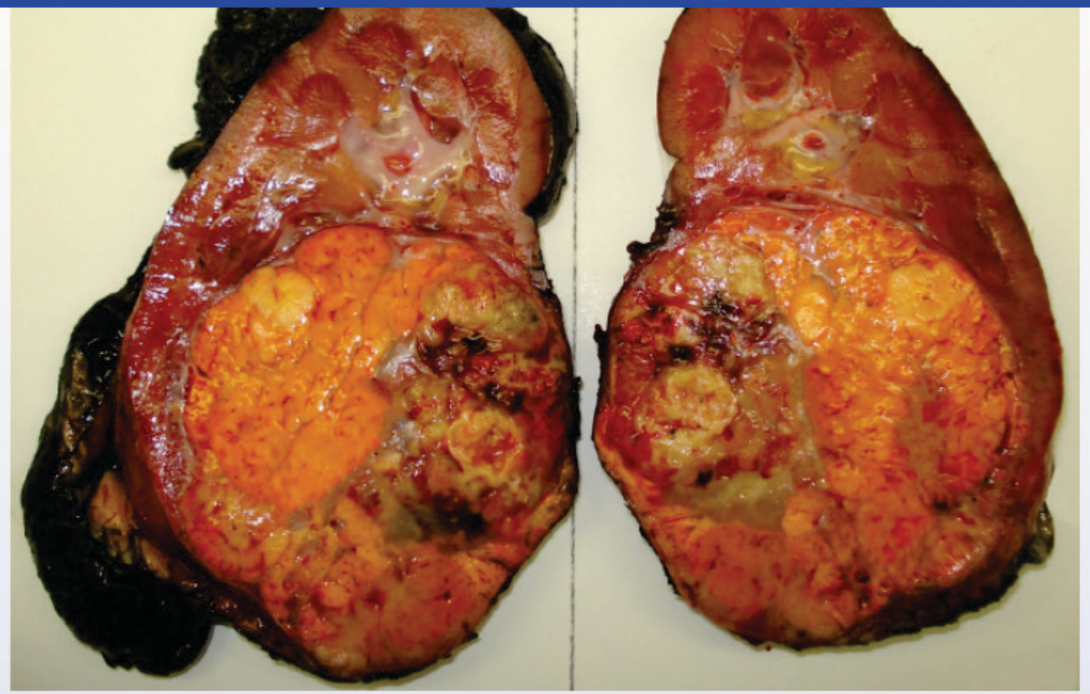


This patient's lesion most likely originated from which of the following portions of the kidney?

- A. Blood vessels
- B. Collecting duct cells
- C. Glomeruli
- D. Proximal renal tubules
- E. Renal pelvis lining

Submit

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This patient's lesion most likely originated from which of the following portions of the kidney?

- A. Blood vessels (7%)
- B. Collecting duct cells (13%)
- C. Glomeruli (4%)
- ✓ D. Proximal renal tubules (48%)
- E. Renal pelvis lining (26%)

Correct

48% Answered correctly

15 secs Time Spent

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Renal cell carcinoma	
Presentation	• Hematuria, flank pain, palpable abdominal mass • Paraneoplastic syndrome (eg, polycythemia, hypercalcemia)
Risk factors	• Smoking, hypertension, obesity • Toxin exposure (eg, heavy metal, petroleum by-products)
Gross examination	• Spherical mass, often with invasion of the renal vein • Golden-yellow tissue (due to high lipid content)
Histology (Clear cell)	• Cuboidal or polygonal cells with abundant, clear cytoplasm • Branching, "chicken-wire" vasculature

This patient with a history of chemical exposure and a necrotic kidney mass likely has renal cell carcinoma (RCC), the most common renal malignancy. RCC originates in the renal cortex and occurs most commonly in patients age 60-70. Risk factors include **smoking**, obesity, hypertension and **toxin exposure** (eg, heavy metal, petroleum by-products, asbestos).

RCC is classified into subtypes based on cellular origin; **clear cell carcinoma** (CCC) is the most common type and accounts for up to 85% of RCCs. CCC originates from the epithelium of the **proximal renal tubules**. Gross pathology typically demonstrates a **sphere-like** mass composed of **golden-yellow tissue** (due to high lipid content) with areas of focal **necrosis** and **hemorrhage**. It often invades the renal vein and may extend into the inferior vena cava. On microscopy, CCC appears as cuboidal or polygonal cells with abundant clear cytoplasm.

(Choice A) Angiomyolipomas are rare tumors that arise from perivascular epithelioid cells. Gross pathology demonstrates a well-circumscribed tumor composed of variable amounts of 3 different tissue types: yellow adipose tissue, red vascular components, and grayish smooth muscle. Angiomyolipomas are benign neoplasms often associated with tuberous sclerosis.

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(Choice B) Renal oncocytomas are rare tumors that originate from collecting duct cells. Gross pathology often demonstrates a homogenous brown tumor with a central stellate scar that is often visible on imaging; focal areas of necrosis are rare.

(Choice C) Glomerular diseases (eg, membranous nephropathy, minimal change disease) can be seen as a paraneoplastic syndrome associated with certain malignancies (eg, lung, gastrointestinal tumors), but the glomeruli are not the site of origin of RCC.

(Choice E) Urothelial carcinoma arises from the epithelium of the renal pelvis, ureters, or bladder and may be multifocal in nature. It often forms papillary tumors composed of urothelium supported by a thin fibrovascular stalk.

Educational objective:
Clear cell carcinoma is the most common type of renal cell carcinoma and originates from the epithelial cells of the proximal renal tubules. Gross pathology typically demonstrates a sphere-like mass composed of golden-yellow

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products, asbestos).

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Educational objective:
Clear cell carcinoma is the most common type of renal cell carcinoma and originates from the epithelial cells of the proximal renal tubules. Gross pathology typically demonstrates a sphere-like mass composed of golden-yellow cells (due to high lipid content) with areas of necrosis and hemorrhage.

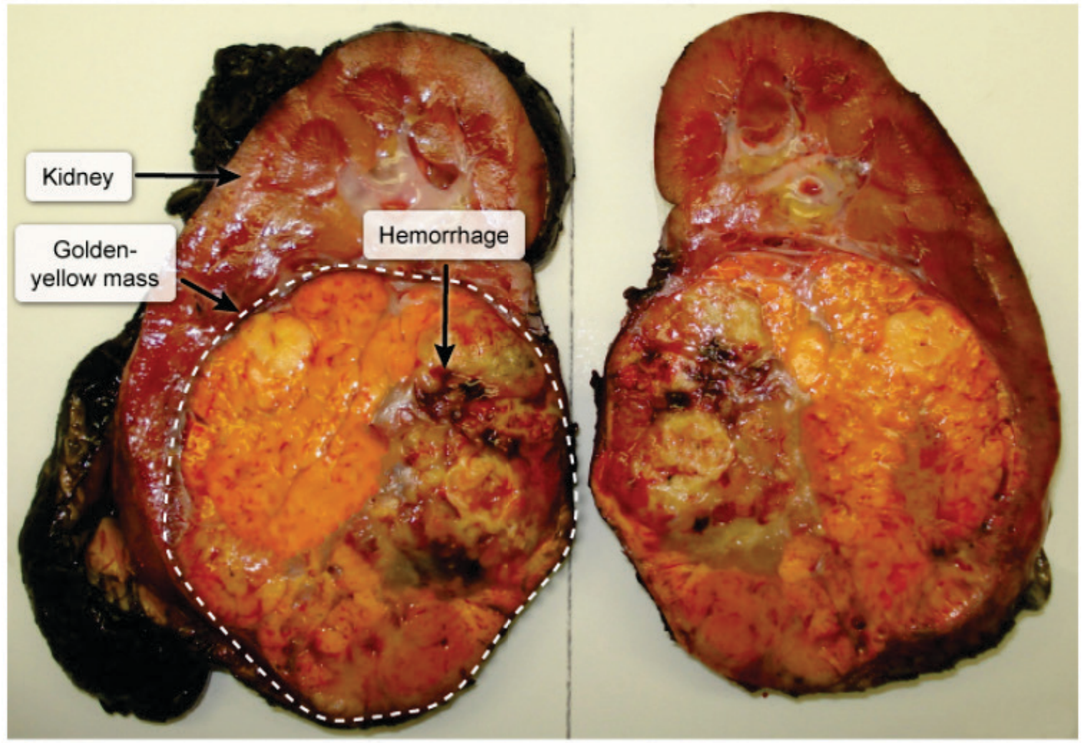
Pathology Renal, Urinary Systems & Electrolytes Renal cell carcinoma

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Histology	• Cuboidal or polygonal cells with abundant, clear cytoplasm

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Clear cell renal cell carcinoma



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Histology	• Cuboidal or polygonal cells with abundant, clear cytoplasm

Exhibit Display

Renal angiomyolipoma



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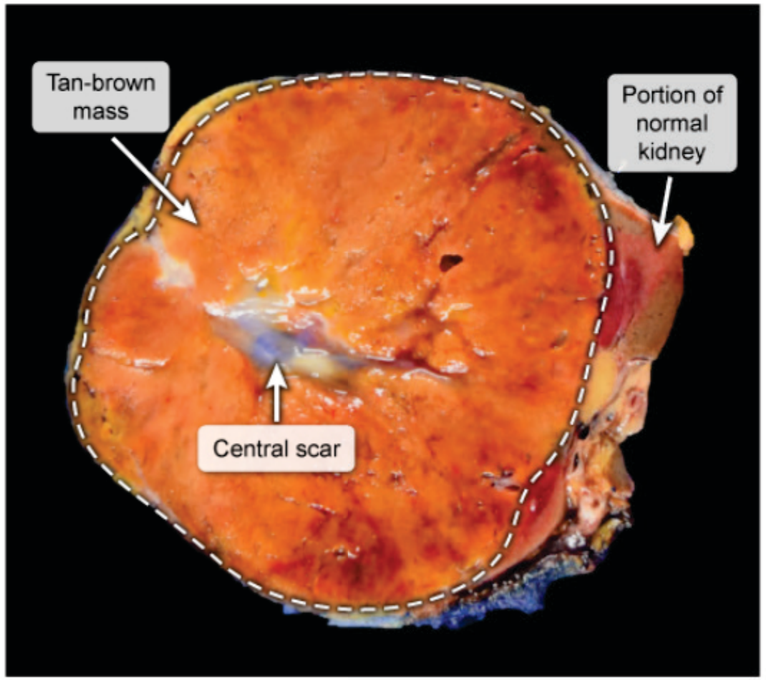
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Histology	• Cuboidal or polygonal cells with abundant, clear cytoplasm

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Renal oncocytoma



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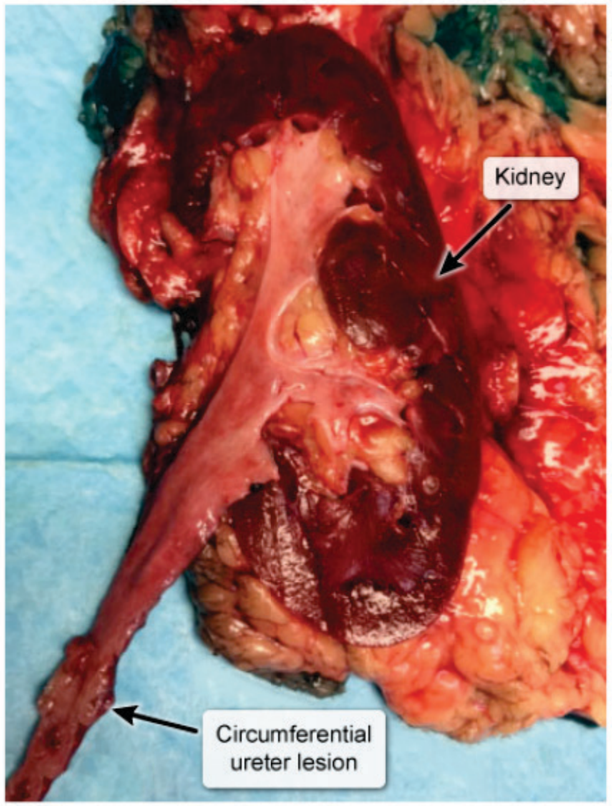
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Urothelial carcinoma of the ureter



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Pathology | Renal, Urinary Systems & Electrolytes | Renal cell carcinoma

https://t.me/USMLEWorldStep1

A group of researchers is studying secondary hypertension in porcine models of renal artery stenosis. During an experiment, a clip is placed that constricts the right renal artery to 30% of its original cross-sectional area. A few days later, hemodynamic and biochemical measurements are recorded and compared to measurements obtained before clip placement. Which of the following changes is most likely to be seen in the experimental animals?

- A. Decreased inferior vena cava aldosterone level
- B. Decreased systemic vascular resistance
- C. Increased glomerular filtration in the right kidney
- D. Increased renin production in the left kidney
- E. Increased sodium excretion in the left kidney

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- A. Decreased inferior vena cava aldosterone level (2%)
- ✗ B. Decreased systemic vascular resistance (5%)
- C. Increased glomerular filtration in the right kidney (26%)
- D. Increased renin production in the left kidney (31%)
- ✓ E. Increased sodium excretion in the left kidney (33%)

Incorrect
Correct answer
E

33%
Answered correctly

03 secs
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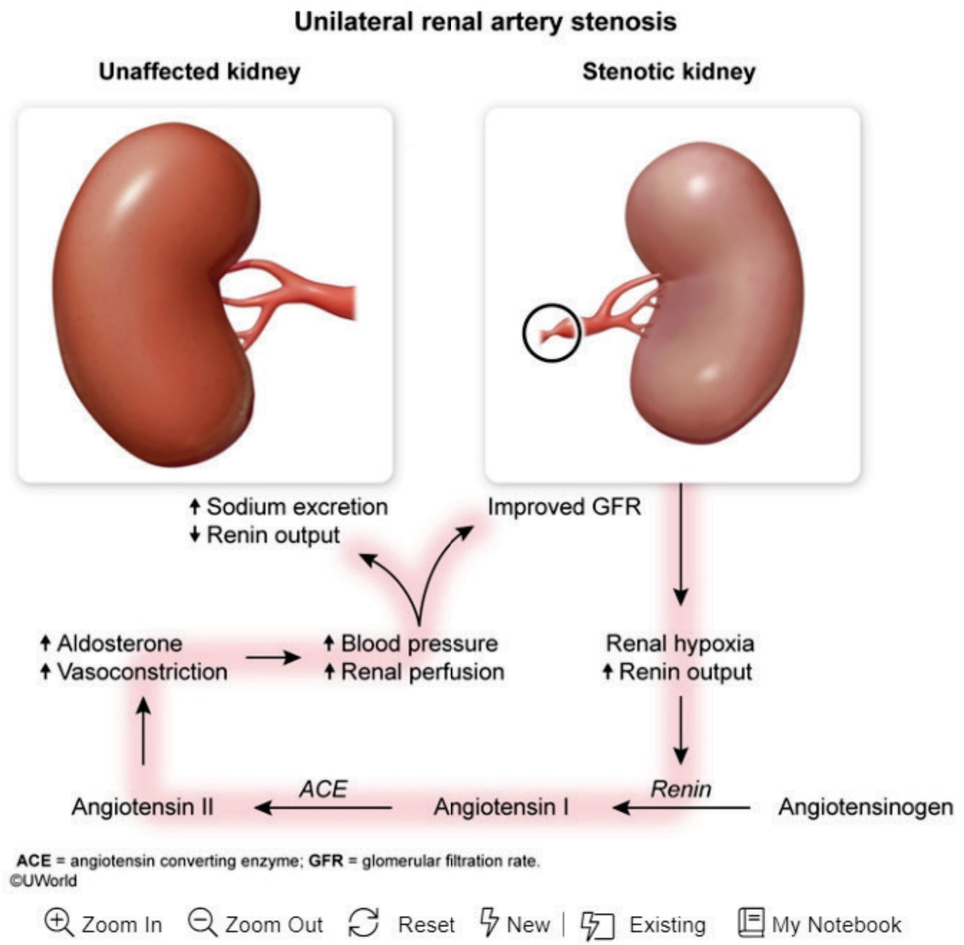
Explanation



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Unilateral renal hypoperfusion (due to **renal artery stenosis** or clipping) causes activation of the **renin-angiotensin-aldosterone system** (RAAS). In response to low perfusion pressures, the juxtaglomerular cells of the kidney synthesize renin, which converts angiotensinogen (synthesized in the liver) to angiotensin I. Angiotensin-converting enzyme, which is synthesized largely in the lungs, then converts angiotensin I to its active form, angiotensin II.

Angiotensin II has multiple actions to increase systemic blood pressure. It directly **increases systemic vascular** resistance through generalized arteriolar vasoconstriction **(Choice B)**. It also increases sodium and water reabsorption both directly, by increasing sodium reabsorption in the proximal tubule, and indirectly, by stimulating **aldosterone** synthesis in the adrenal cortex and antidiuretic hormone in the hypothalamus **(Choice A)**. Elevated systemic pressure and blood volume help overcome the decreased perfusion pressures in the stenotic kidney and maintain a near-normal filtration rate.

However, the **unaffected kidney** is exposed to elevated systemic pressures, resulting in **increased sodium excretion** due to a pressure natriuresis effect. Although this helps reduce circulating volume, many patients with renal artery stenosis have **chronic hypertension** due to persistent hyperreninemia and angiotensin II–induced vasoconstriction caused by the stenotic kidney.

(Choice C) After placement of the clip, glomerular filtration rate will drop in the stenotic kidney, triggering compensatory RAAS activation. This increases the perfusion pressure of the stenotic kidney, helping to normalize glomerular filtration rate. However, like most compensatory responses, the increase in filtration caused by RAAS activation is not enough to overcome the initial drop in filtration caused by clip placement. Therefore, the filtration rate remains less than normal in the stenotic kidney.

(Choice D) Renin production is suppressed in the unaffected kidney due to its exposure to elevated systemic pressures.

Educational objective:

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Educational objective:
Unilateral renal artery stenosis causes hypoperfusion and activation of the renin-angiotensin-aldosterone system. Angiotensin II causes arteriolar vasoconstriction and increases aldosterone and antidiuretic hormone synthesis. The resultant hypertension helps reduce the decline in glomerular filtration rate in the affected kidney, but causes a pressure natriuresis with increased sodium excretion in the unaffected kidney.

Physiology	Renal, Urinary Systems & Electrolytes	Renal artery stenosis
Subject	System	Topic

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A 36-year-old woman with end-stage renal disease secondary to type 1 diabetes mellitus comes to the office for routine examination. The patient's medical history includes hypertension, diabetic retinopathy, and neuropathy. Hemodialysis was started 2 months ago along with an erythropoiesis-stimulating agent. She takes daily long- and short-acting insulin, lisinopril, and calcitriol. Her hemoglobin has increased from 7.4 g/dL to 10.2 g/dL over the past 2 months. Which of the following complications is most likely to be seen with the agent used to treat this patient's anemia?

- A. Angioedema
- B. Diarrhea
- C. Hyperkalemia
- D. Hypoglycemia
- E. Mineral bone disease
- F. Worsening hypertension

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- B. Diarrhea
- C. Hyperkalemia
- D. Hypoglycemia
- E. Mineral bone disease
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A 36-year-old woman with end-stage renal disease secondary to type 1 diabetes mellitus comes to the office for routine examination. The patient's medical history includes hypertension, diabetic retinopathy, and neuropathy. Hemodialysis was started 2 months ago along with an erythropoiesis-stimulating agent. She takes daily long- and short-acting insulin, lisinopril, and calcitriol. Her hemoglobin has increased from 7.4 g/dL to 10.2 g/dL over the past 2 months. Which of the following complications is most likely to be seen with the agent used to treat this patient's anemia?

- A. Angioedema (10%)
- ✗ B. Diarrhea (4%)
- C. Hyperkalemia (11%)
- D. Hypoglycemia (6%)
- E. Mineral bone disease (16%)
- ✓ F. Worsening hypertension (50%)

Incorrect
Correct answer
F

50%
Answered correctly

19 secs
Time Spent

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Version

Explanation

Erythropoiesis-stimulating agents (ESAs) (eg, erythropoietin, darbepoetin alpha) can be used to treat **anemia of chronic kidney disease** (CKD), which usually develops at a glomerular filtration rate of <30 mL/min. Untreated anemia in CKD and dialysis patients can lead to cardiac dysfunction, fatigue, weakness, and possible mental status changes (eg, decreased cognition). ESAs can substantially improve anemia, avoiding the need for blood

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Erythropoiesis-stimulating agents (ESAs) (eg, erythropoietin, darbepoetin alpha) can be used to treat **anemia of chronic kidney disease** (CKD), which usually develops at a glomerular filtration rate of <30 mL/min. Untreated anemia in CKD and dialysis patients can lead to cardiac dysfunction, fatigue, weakness, and possible mental status changes (eg, decreased cognition). ESAs can substantially improve anemia, avoiding the need for blood transfusions. However, ESAs are associated with increased risk for **thromboembolic events** (eg, vascular graft thrombosis, stroke) due to increased blood viscosity, as a result of the elevation in red cell mass. Many patients also develop **hypertension**, possibly due to activation of erythropoietin receptors on vascular endothelial and smooth muscle cells.

(Choice A) Angioedema is a possible side effect of lisinopril, an ACE inhibitor. ACE inhibition causes impaired inactivation of bradykinin (a vasoactive peptide), leading to vasodilation, hypotension, and possible angioedema.

(Choices B and D) Iron supplements can cause constipation, diarrhea, nausea, and epigastric pain. Long-acting insulin is usually cleared by the kidneys and can predispose CKD patients to hypoglycemia. However, ESAs are usually not associated with diarrhea or hypoglycemia.

(Choice C) Hyperkalemia is a frequent complication of acute kidney disease and CKD. However, it is not a common side effect of ESAs.

(Choice E) Mineral bone disease can be a complication of CKD due to secondary hyperparathyroidism, leading to calcium loss from bone. However, it is not a side effect of this patient's medications.

Educational objective:
Erythropoiesis-stimulating agents (ESAs) can substantially improve anemia symptoms, avoiding the need for blood transfusions in chronic kidney disease and dialysis patients. However, ESAs are associated with increased risk for hypertension and thromboembolic events.

References

- The cardiovascular effects of erythropoietin.

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A 23-year-old hiker loses a foothold and falls several feet during a mountain climb. He sustains no major injury but loses his backpack. He walks in the heat without water for the next 8 hours; by the time he reaches a shelter, he is extremely thirsty. Fluid from which of the following nephron segments is likely to be the most hypoosmotic in this individual?

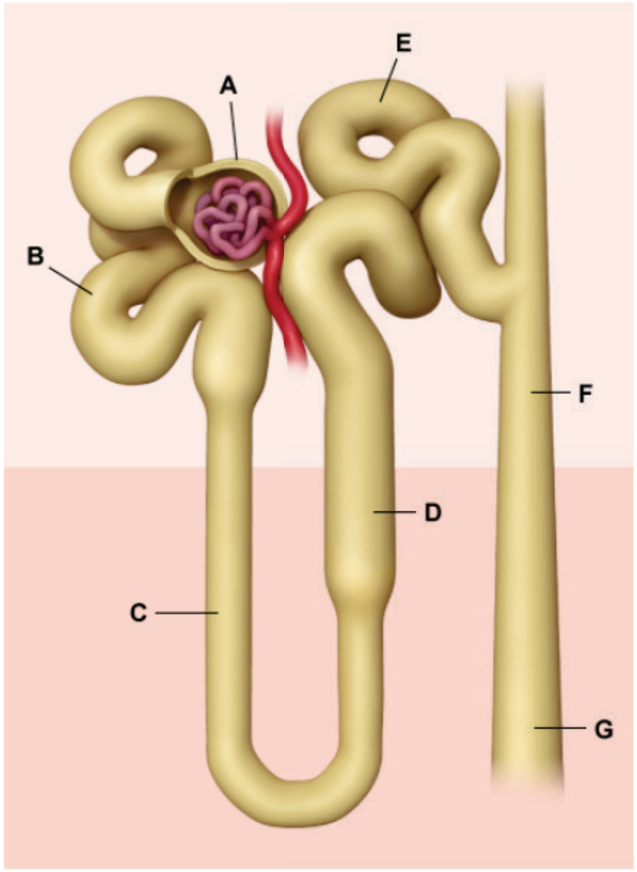
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- F. F
- G. G

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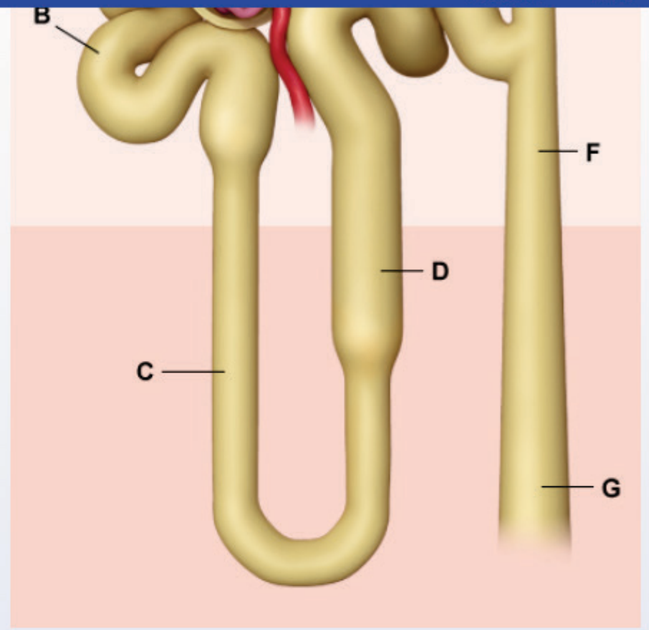
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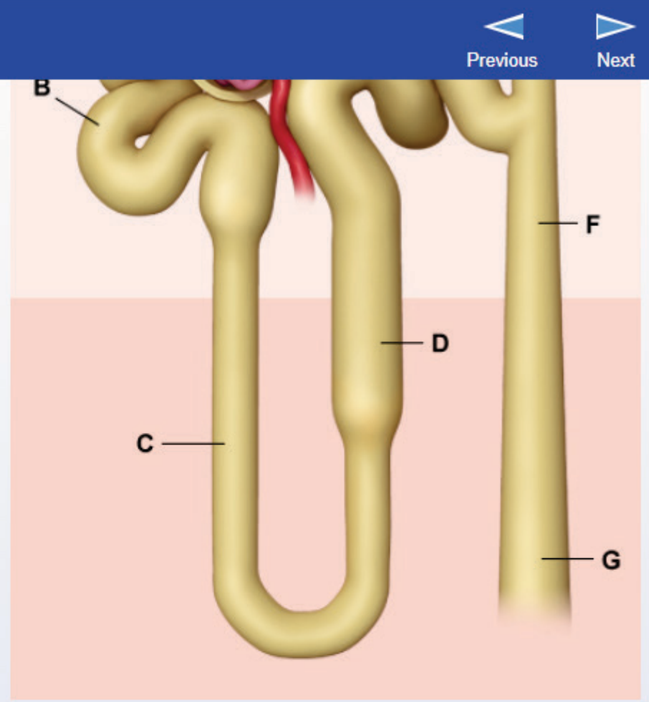
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- A. A
- B. B
- C. C
- D. D
- E. E
- F. F
- G. G

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- A. A (5%)
- B. B (7%)
- ✗ C. C (9%)
- D. D (17%)
- ✓ E. E (43%)
- F. F (6%)
- G. G (10%)

Incorrect
Correct answer
E

43%
Answered correctly

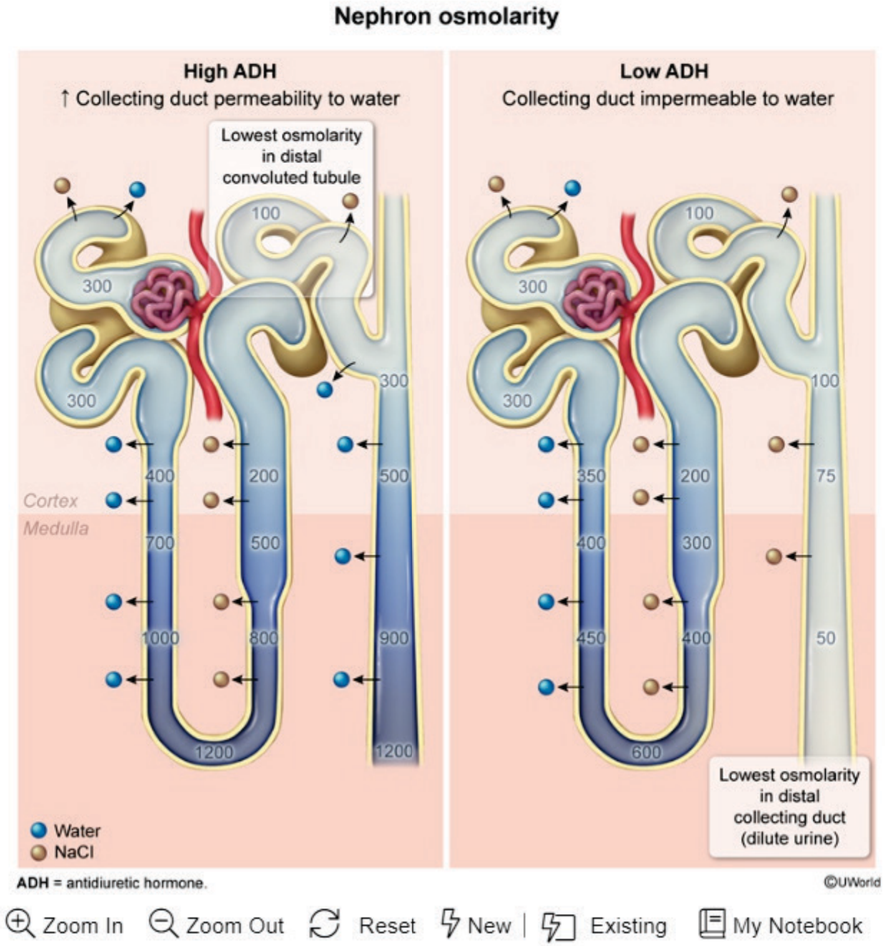
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Explanation

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The following changes in osmolarity occur as glomerular filtrate transits the nephron:

- Glomerular capillaries are highly permeable to water and other solutes, producing filtrate in the Bowman space that is roughly isoosmolar with plasma (~275-300 mOsm/L).
- The proximal convoluted tubule actively reabsorbs electrolytes, glucose, and amino acids; water follows passively, and lumenal osmolarity remains unchanged.
- In the descending limb of the loop of Henle, water is reabsorbed passively into the hypertonic renal interstitium; tubular fluid osmolarity increases (~1,200 mOsm/L).
- The thin and thick ascending limbs of the loop of Henle are impermeable to water, but electrolytes (primarily sodium and chloride) are actively reabsorbed in large quantities, leading to increasingly dilute tubular fluid. When the fluid reaches the initial part of the **distal convoluted tubule**, it will be at its **lowest osmolarity** (~100 mOsm/L) up to that point in the nephron **(Choices A, B, C, and D)**.
- Reabsorption of water in the latter part of the distal tubule and collecting duct is variable and regulated by **antidiuretic hormone** (ADH). At baseline (ie, well hydrated), water permeability of the ductal epithelium is low, leading to production of dilute urine. However, in the dehydrated state (eg, hypotension, high plasma osmolarity), secretion of ADH increases, greatly enhancing permeability of the collecting duct to water and rapidly **concentrating the urine**.

This **dehydrated individual** likely has high circulating ADH levels to help minimize further fluid loss. Therefore, the fluid leaving the early **distal tubular segment** will be the **most hypoosmotic**; in the latter part of the distal tubule and collecting duct, ADH will facilitate diffusion of water into the hypertonic medullary interstitium and urine concentration will rise up to 1,200-1,400 mOsm/L **(Choices F and G)**.

Educational objective:
Dehydration (eg, hypotension, high plasma osmolarity) increases circulating levels of antidiuretic hormone, increasing the water permeability of the collecting duct and allowing production of highly concentrated urine. In the

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space that is roughly isoosmolar with plasma (~275-300 mOsm/L).

- The proximal convoluted tubule actively reabsorbs electrolytes, glucose, and amino acids; water follows passively, and lumenal osmolarity remains unchanged.
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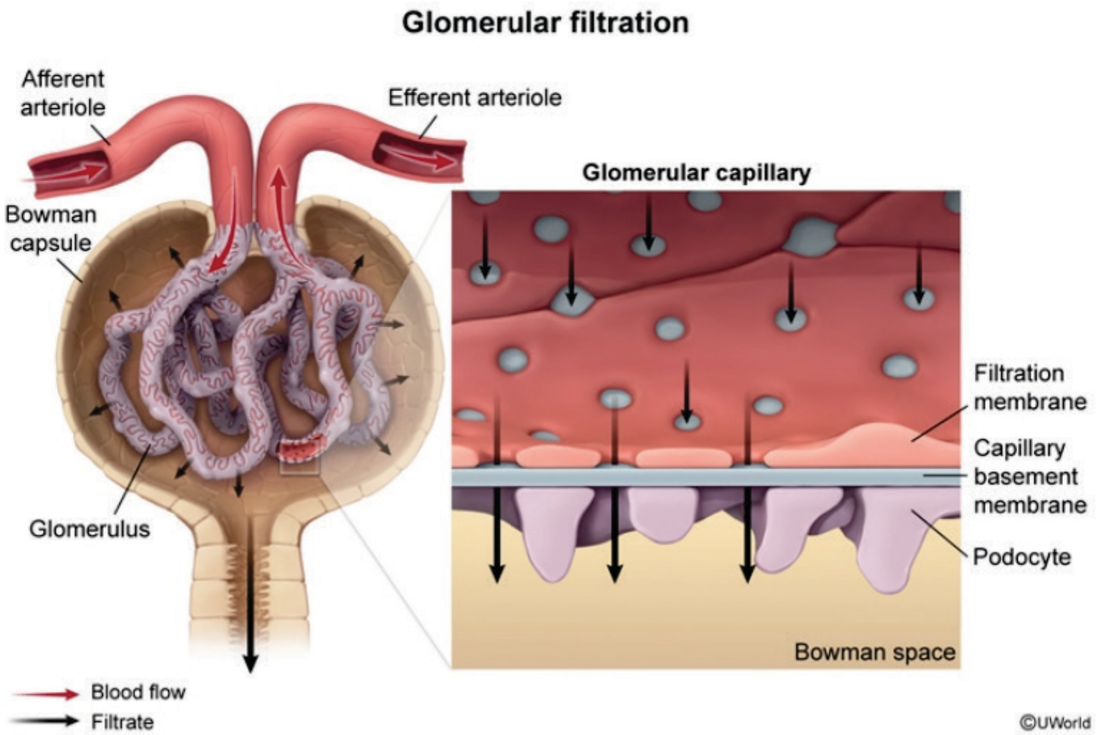
Educational objective:
Dehydration (eg, hypotension, high plasma osmolarity) increases circulating levels of antidiuretic hormone, increasing the water permeability of the collecting duct and allowing production of highly concentrated urine. In the dehydrated state, tubular fluid osmolarity will be lowest at the beginning of the distal convoluted tubule (ie, terminus of loop of Henle).

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Lowest osmolarity in distal

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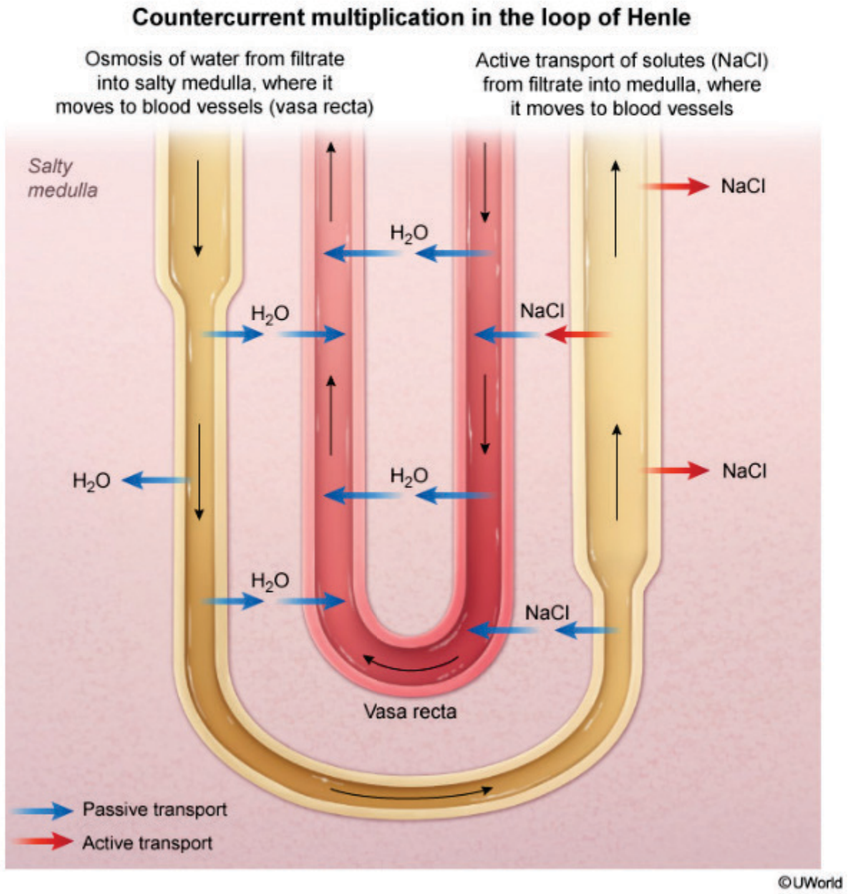
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Lowest osmolarity in distal

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A 37-year-old woman comes to the office due to worsening leg swelling for the past 2 months. She has also felt excessively tired and has had achy pain in her hands. Temperature is 37.3 C (99.1 F), blood pressure is 156/92 mm Hg, and pulse is 86/min. BMI is 32 kg/m^2. Physical examination shows 2+ pitting bilateral edema in the lower extremities. Bilateral finger joints and wrists are mildly swollen and tender to palpation. Serum creatinine level is 1.8 mg/dL. Urinalysis is positive for proteinuria and hematuria. Light microscopy of samples from a kidney biopsy shows diffuse, global endocapillary hypercellularity. Direct immunofluorescence demonstrates "full-house" staining with diffuse, global, granular staining of glomerular capillary walls by IgG, IgM, IgA, C1q, and C3. Electron microscopy shows abundant subendothelial electron-dense deposits. Which of the following is the most likely underlying cause of this patient's renal disease?

- A. Granulomatosis with polyangiitis
- B. Group A *Streptococcus* infection
- C. Multiple myeloma
- D. Rheumatoid arthritis
- E. Systemic lupus erythematosus

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- A. Granulomatosis with polyangiitis (5%)
- ✗ B. Group A *Streptococcus* infection (7%)
- C. Multiple myeloma (2%)
- D. Rheumatoid arthritis (7%)
- ✓ E. Systemic lupus erythematosus (76%)

Incorrect
Correct answer
E

76%
Answered correctly

04 secs
Time Spent

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Version

Explanation

This patient's hematuria with proteinuria, renal insufficiency (elevated creatinine), and sodium/fluid retention (hypertension and edema) are indicative of **glomerulonephritis** (GN). Although GN has many etiologies, the patient's tender and swollen hand joints (**inflammatory arthritis**) and renal biopsy findings are strongly suggestive

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Explanation

This patient's hematuria with proteinuria, renal insufficiency (elevated creatinine), and sodium/fluid retention (hypertension and edema) are indicative of **glomerulonephritis** (GN). Although GN has many etiologies, the patient's tender and swollen hand joints (**inflammatory arthritis**) and renal biopsy findings are strongly suggestive of underlying **systemic lupus erythematosus**.

An immunofluorescence pattern containing **IgG, IgM, IgA** and **C3, C1q** is highly characteristic of lupus nephritis and is referred to as a **full-house** (ie, a poker hand with three of a kind [3 immunoglobulin classes] and two of a kind [2 complement components]). The full-house pattern reflects the pathogenesis of lupus: loss of immune tolerance to self-antigens (eg, double-stranded DNA) leads to generation of **polyclonal autoantibodies** that form circulating immune complexes; these deposit in the glomeruli, where they cause local injury by activating the **classical complement** cascade.

Immune complex deposition in the subendothelial space (visible on electron microscopy) allows for direct contact with inflammatory cells (eg, neutrophils), causing glomerular inflammation. The resulting leukocyte infiltration is seen on light microscopy as endocapillary hypercellularity.

(Choice A) Granulomatosis with polyangiitis is an antineutrophil cytoplasmic antibody–associated vasculitis that can cause GN and arthritis. However, there is characteristically a lack of immunoglobulin or complement (ie, pauci-immune) on immunofluorescence.

(Choice B) Group A *Streptococcus* infection can result in poststreptococcal GN (PSGN). Although LM reveals endocapillary hypercellularity, immunofluorescence contains mostly IgG and C3 deposits (vs a full house). Moreover, PSGN is usually preceded by throat or skin infections, and arthritis is atypical.

(Choice C) Renal disease in multiple myeloma most commonly results from excessive secretion of immunoglobulin light chains (eg, kappa) that form obstructing casts within the renal tubules. Glomerular deposition of multiple immunoglobulin classes and complement components would be unexpected.

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(Choice D) Although rheumatoid arthritis is characterized by small joint inflammatory arthritis, GN is rare, and immunofluorescence would not be expected to show a full-house pattern.

Educational objective:
Lupus nephritis from systemic lupus erythematosus can manifest as glomerulonephritis. Immunofluorescence microscopy showing a full house with 3 immunoglobulin classes (IgG, IgM, IgA) and 2 complement components (C3, C1q) is highly characteristic.

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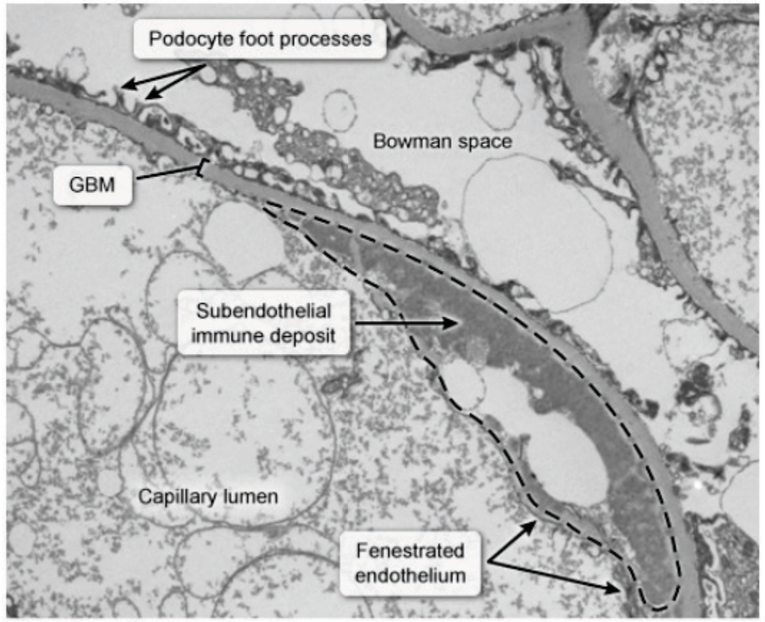
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(C3, C1q) is highly characteristic.

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Subendothelial immune deposits in lupus nephritis



GBM = glomerular basement membrane. ©UWorld

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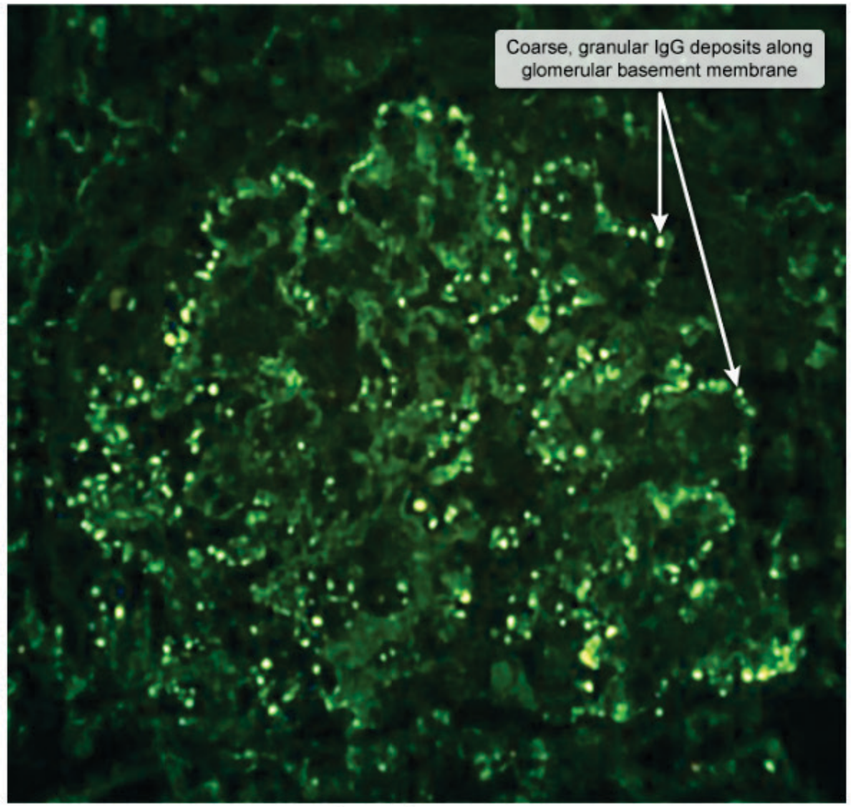
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(C3, C1q) is highly characteristic.

Exhibit Display

Poststreptococcal glomerulonephritis



Immunofluorescence

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A 47-year-old man is treated for bacterial sinusitis with ampicillin. A week later he comes to the emergency department with fever and a skin rash. He also reports low urine output. Temperature is 37.5 C (99.5 F), blood pressure is 123/71 mm Hg, and pulse is 88/min. Physical examination shows a diffuse maculopapular rash. Serum creatinine level is 2.4 mg/dL, and urine sediment microscopy reveals 3-4 red blood cells/hpf, 5-10 white blood cells/hpf, and 3-5 eosinophils/hpf. The pathologic process affecting this patient's kidneys most likely involves which of the following structures?

- A. Calyces and ureters
- B. Glomeruli
- C. Renal interstitium
- D. Renal papillae
- E. Small renal arterioles

Submit

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- A. Calyces and ureters (2%)
- ✗ B. Glomeruli (21%)
- ✓ C. Renal interstitium (62%)
- D. Renal papillae (11%)
- E. Small renal arterioles (2%)

Incorrect
Correct answer
C

62%
Answered correctly

05 secs
Time Spent

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Explanation

Acute interstitial nephritis	
Causes	• **Antibiotics** (eg, beta-lactam, sulfonamide, rifampin) • Proton pump inhibitors • NSAIDs • Diuretics

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Acute interstitial nephritis	
Causes	• **Antibiotics** (eg, beta-lactam, sulfonamide, rifampin) • Proton pump inhibitors • NSAIDs • Diuretics • Other: Autoimmune diseases, *Mycoplasma*, *Legionella*
Clinical features	• Rash, fever, or asymptomatic • New drug exposure
Laboratory findings	• Acute kidney injury • Pyuria, hematuria, WBC casts • Eosinophilia, **urinary eosinophils** • Renal biopsy: Inflammatory interstitial infiltrate and edema
NSAIDs = nonsteroidal anti-inflammatory drugs; **WBC** = white blood cell.	

Fever, maculopapular rash, and acute renal failure (eg, elevated creatinine, oliguria) occurring within a few weeks of starting a **beta-lactam antibiotic** are highly suggestive of drug-induced **acute interstitial nephritis** (AIN). Other commonly implicated medications include nonsteroidal anti-inflammatory drugs, sulfonamides, rifampin, proton pump inhibitors, and diuretics. Many patients have increased levels of serum eosinophils and **eosinophiluria** (detected by Hansel or Wright stain). Urinalysis may also show white blood cells, white blood cell casts, and red blood cells. Symptoms most commonly occur **1-3 weeks after drug initiation** and typically resolve with cessation of the offending medication.

AIN is thought to be due to IgE-mediated (type I) or cell-mediated (type IV) hypersensitivity. It primarily involves the **renal interstitium**, causing interstitial edema and **leukocyte infiltration** (particularly lymphocytes,

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(Choice A) Calyces and ureters are most commonly involved in nephrolithiasis and associated hydronephrosis, which can cause hematuria and renal failure. However, nephrolithiasis typically causes flank pain; fever, rash, and eosinophiluria would be unexpected.

(Choice B) Glomeruli are involved in poststreptococcal glomerulonephritis, which can cause acute kidney injury 1-3 weeks after infection with group A beta-hemolytic streptococcus. However, dysmorphic red blood cells and/or red blood cell casts would be expected in a nephritic disease; eosinophiluria, fever, and rash are more consistent with AIN.

(Choice D) Pathology affecting the renal papillae (papillary necrosis) is common in severe, acute pyelonephritis and in patients with sickle cell disease, diabetes mellitus, or analgesic nephropathy. Urinalysis shows hematuria or sterile pyuria, but rash and eosinophiluria are unexpected.

(Choice E) Small renal arterioles are not involved in AIN. They are most commonly damaged in hypertensive or diabetic nephropathy, which typically presents with proteinuria, not with pyuria and urinary eosinophils.

Educational objective:

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Educational objective:
Fever, maculopapular rash, and acute renal failure occurring 1-3 weeks after beginning a new medication (eg, antibiotics, proton pump inhibitors) is highly suggestive of acute interstitial nephritis. Peripheral eosinophilia, sterile pyuria, eosinophiluria, and white blood cell casts may also be seen. Histology reveals leukocyte infiltration and edema of the renal interstitium.

References

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Physiologists are studying how the plasma concentration of various substances affects the degree to which they are excreted in the urine. During one experiment, a substance freely filtered at the glomerulus is infused intravenously at various rates. The plasma concentration (mg/mL) and urinary excretion rate (mg/min) of the substance are monitored. Assuming a constant glomerular filtration rate (GFR) of 100 mL/min, the following observations are made:

	Preinfusion	Low-dose infusion	Medium-dose infusion	High-dose infusion
Filtered load (mg/min) (GFR × plasma concentration)	100	200	400	600
Urinary excretion rate (mg/min)	0	100	300	500

Which of the following substances is most likely to demonstrate a similar pattern of filtration and excretion in a healthy adult?

- A. Albumin
- B. Creatinine
- C. Glucose
- D. Mannitol
- E. Urea

Submit

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	Preinfusion	Low-dose infusion	Medium-dose infusion	High-dose infusion
Filtered load (mg/min) (GFR × plasma concentration)	100	200	400	600
Urinary excretion rate (mg/min)	0	100	300	500

Which of the following substances is most likely to demonstrate a similar pattern of filtration and excretion in a healthy adult?

- A. Albumin (1%)
- ✗ B. Creatinine (26%)
- ✓ C. Glucose (43%)
- D. Mannitol (8%)
- E. Urea (19%)

Incorrect
Correct answer

43%

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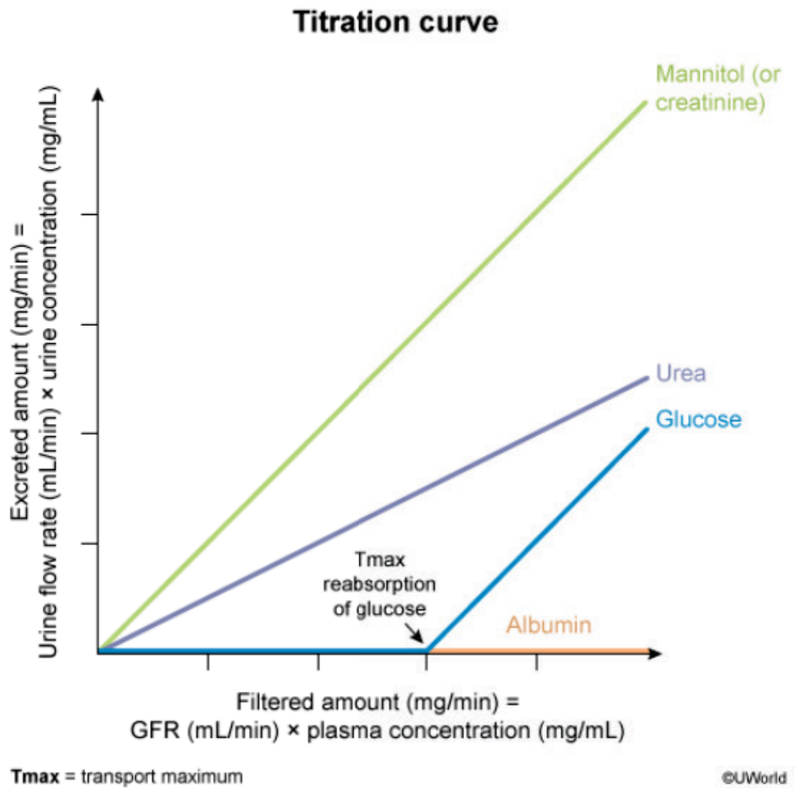
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reabsorbed, and no amount is excreted in the urine. However, as the concentration and filtered load are
increased, the substance begins to spill into the urine, suggesting a **limit to the rate** at which it can be

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At physiologic levels (preinfusion), the experimental substance is filtered at the glomerulus but completely reabsorbed, and no amount is excreted in the urine. However, as the concentration and filtered load are increased, the substance begins to spill into the urine, suggesting a **limit to the rate** at which it can be **reabsorbed**. This rate, called the **transport maximum** (Tmax) of a substance, is determined by the capacity of transporters available for active reabsorption.

The reabsorption pattern is **similar** to that of **glucose**, which is **filtered in the glomerulus** and **reabsorbed completely** in the proximal tubule under normal serum concentrations. However, once glucose reaches its Tmax, the excess filtered load passes unabsorbed through the tubules. The serum concentration at which glucosuria begins, called the threshold of glucose, is approximately **200 mg/dL**.

(Choice A) Albumin is a large, polarized plasma protein that is not filtered in a normal, healthy glomerulus, so urinary excretion would remain at 0 mg/min.

(Choices B and D) Creatinine and mannitol (an osmotic diuretic) are freely filtered in the glomerulus and are not reabsorbed. As a result, the urinary excretion of these substances is dependent on the glomerular filtration rate and remains equal to the filtered load of the substance regardless of the serum concentration (note that urinary excretion of creatinine is slightly more than the filtered rate due to tubular secretion).

(Choice E) Urea is filtered and then reabsorbed by passive diffusion into the peritubular capillaries. Approximately 20%-50% of the filtered load is normally reabsorbed. Urea has no Tmax because it is passively reabsorbed.

Educational objective:
At normal plasma concentrations of glucose, the renal tubules reabsorb the entire filtered load of glucose because it is below the maximum tubular reabsorption ability (transport maximum of glucose). At higher plasma concentrations, glucose is excreted when the filtered amount exceeds the transport maximum. The serum concentration at which glucosuria begins, called the threshold of glucose, is approximately 200 mg/dL.

Physiology Renal, Urinary Systems & Electrolytes GFR

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A newborn undergoes an abdominal ultrasound that shows kidneys of normal size, structure, and location. The patient does not appear to be in distress, and physical examination reveals no abnormalities. If this patient were to be diagnosed with renal disease later in life, it would most likely be which of the following?

- A. Autosomal dominant polycystic renal disease
- B. Autosomal recessive polycystic renal disease
- C. Horseshoe kidney
- D. Multicystic dysplastic kidney
- E. Potter sequence

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A newborn undergoes an abdominal ultrasound that shows kidneys of normal size, structure, and location. The patient does not appear to be in distress, and physical examination reveals no abnormalities. If this patient were to be diagnosed with renal disease later in life, it would most likely be which of the following?

- ✓ A. Autosomal dominant polycystic renal disease (73%)
- B. Autosomal recessive polycystic renal disease (17%)
- ✗ C. Horseshoe kidney (1%)
- D. Multicystic dysplastic kidney (7%)
- E. Potter sequence (0%)

Incorrect
Correct answer
A

73%
Answered correctly

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Explanation

Autosomal dominant polycystic kidney disease	
Pathologic features	• Mutations in *PKD-1* or *PKD-2* cause tubular cell proliferation & fluid secretion • Cyst formation occurs at any point in the nephron, but <5% of nephrons are affected • Microscopic cysts present at birth progressively enlarge over the decades • Enlarged cysts compress the renal parenchyma, causing atrophy & fibrosis
Clinical features	• Frequently clinically silent, with 50% of patients going undiagnosed • Symptoms are variable & include flank pain, hematuria & hypertension

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Explanation

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Clinical features	• Frequently clinically silent, with 50% of patients going undiagnosed • Symptoms are variable & include flank pain, hematuria & hypertension • Renal failure slowly progresses over 10-20 years, with end-stage renal disease often occurring by age 70 • Extrarenal manifestations include liver cysts & cerebral aneurysms

Autosomal dominant polycystic kidney disease (ADPKD), like many autosomal dominant diseases, **manifests later in life** (eg, age 40-50). Microscopic cysts are present at birth but are too small to be detected by abdominal ultrasound. Over the years, the cysts enlarge, compression of the renal parenchyma occurs, and patients become symptomatic (eg, flank pain, hypertension).

In contrast, autosomal **recessive** polycystic kidney disease (ARPKD) **presents at birth** or during the first year of life with bilateral flank masses. Cysts are formed by dilated distal tubules and collecting ducts. Abdominal ultrasonography demonstrates enlarged kidneys at birth and often shows cysts, which are visualized if they are >1 cm in diameter **(Choice B)**.

(Choice C) The abnormal fusion of kidneys at their poles (usually the lower poles) is called horseshoe kidney. The isthmus of renal tissue is anterior to the great vessels and is easily detected on abdominal ultrasound.

(Choice D) Multicystic dysplastic kidney is characterized by the presence of multiple renal cysts of varying sizes

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(Choice C) The abnormal fusion of kidneys at their poles (usually the lower poles) is called horseshoe kidney. The isthmus of renal tissue is anterior to the great vessels and is easily detected on abdominal ultrasound.

(Choice D) Multicystic dysplastic kidney is characterized by the presence of multiple renal cysts of varying sizes and the absence of a normal pelvicalyceal system. The condition is associated with ureteral or ureteropelvic atresia, with the affected kidney essentially rendered nonfunctional. Abdominal ultrasound of the fetus or newborn is typically diagnostic.

(Choice E) A number of fetal renal abnormalities (eg, bilateral renal agenesis, ARPKD) can cause a decrease in fetal urine production and oligohydramnios. The combination of abnormalities that ensues, called Potter sequence, includes pulmonary hypoplasia, Potter facies (flattened nose, recessed chin, prominent epicanthal folds, and low-set ears), limb deformities, and cardiovascular abnormalities. Renal defects that lead to Potter sequence are usually profound and easily seen on ultrasound.

Educational objective:
Autosomal dominant polycystic kidney disease typically manifests in patients age 40-50 with enlarged kidneys, flank pain, and hypertension. In newborns, the kidneys are of normal size, and the cysts are too small to be detected on abdominal ultrasonography. As the cysts enlarge, they compress the renal parenchyma and cause symptoms.

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Autosomal dominant polycystic kidney disease (ADPKD), like many autosomal dominant diseases, **manifests**

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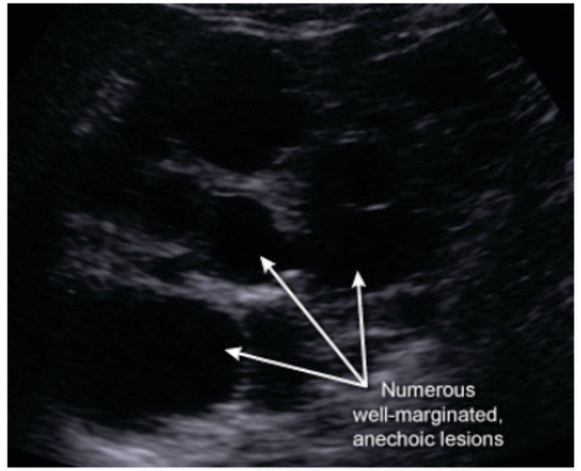
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Renal cysts on ultrasonography



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Autosomal dominant polycystic kidney disease (ADPKD), like many autosomal dominant diseases, **manifests**

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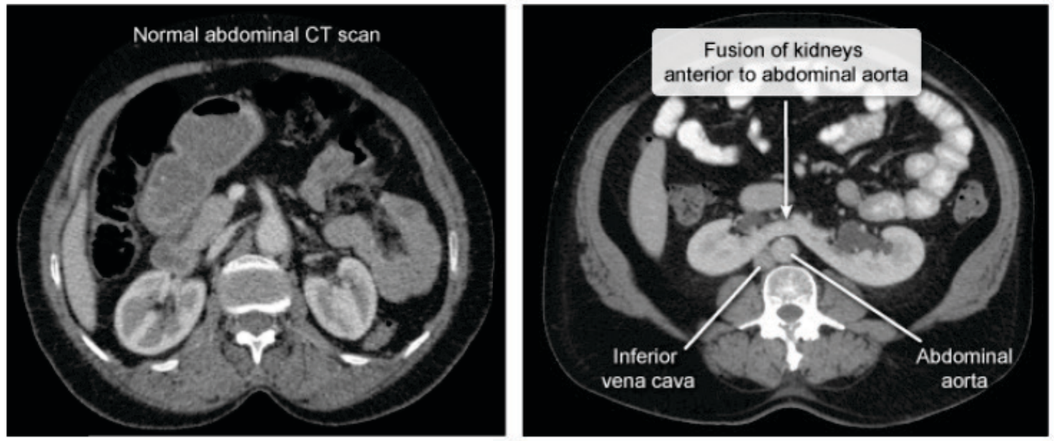
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Horseshoe kidney



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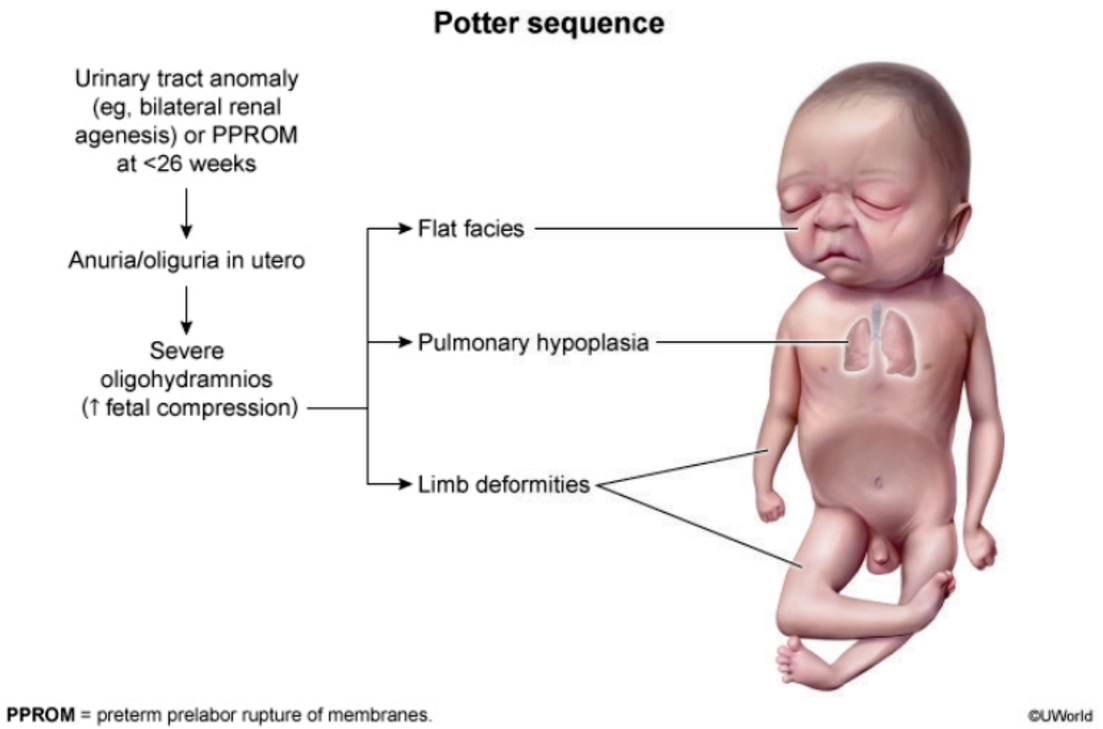
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A 26-year-old woman dies shortly after a sudden-onset, severe headache. She was recently diagnosed with hypertension but otherwise had no medical problems. The patient was a lifetime nonsmoker and did not use illicit drugs. Autopsy reveals evidence of intracranial hemorrhage. Both carotid arteries appear tortuous distally with alternating areas of fibrotic webs and aneurysmal dilation. On microscopic examination, the aneurysmal segments of the carotid arteries lack an internal elastic lamina. Which of the following is the most likely additional finding in this patient?

- A. Adrenal tumor
- B. Coarctation of the aorta
- C. Hypertrophic cardiomyopathy
- D. Renal artery stenosis
- E. Thyroid follicular hyperplasia

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- A. Adrenal tumor (6%)
- ✗ B. Coarctation of the aorta (33%)
- C. Hypertrophic cardiomyopathy (6%)
- ✓ D. Renal artery stenosis (51%)
- E. Thyroid follicular hyperplasia (1%)

Incorrect
Correct answer
D

51%
Answered correctly

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Explanation

Fibromuscular dysplasia	
Manifestations	• Fibromuscular webs (luminal stenosis) alternating with areas of aneurysmal dilation • Loss of the internal elastic lamina • Most common in women, age <55

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Fibromuscular dysplasia	
Manifestations	• Fibromuscular webs (luminal stenosis) alternating with areas of aneurysmal dilation • Loss of the internal elastic lamina • Most common in women, age <55
Presentation	• Resistant hypertension (RAS) • CNS involvement: Headache, TIA, stroke, ruptured aneurysm
Diagnosis	• Angiography (CT, MRI, percutaneous) • String-of-beads appearance (multifocal disease)
RAS = renal artery stenosis; **TIA** = transient ischemic attack.	

This young woman with recent-onset hypertension died of an intracranial hemorrhage, likely from a ruptured aneurysm. This, in conjunction with the characteristic pathology findings of **fibromuscular webs** alternating with **aneurysmal dilation** and loss of the internal elastic lamina, is consistent with **fibromuscular dysplasia** (FMD). FMD is a nonatherosclerotic disease characterized by abnormal tissue growth within arterial walls, leading to arterial stenosis, tortuosity, aneurysms, or dissections. FMD typically occurs in women age <55. Angiography (ie, percutaneous, CT, MRI) is diagnostic and typically demonstrates a **string-of-beads** appearance in multifocal disease.

FMD can involve any artery but most commonly the renal, cerebral (eg, carotid, vertebral), and visceral arteries. Up to 80% of patients develop **renal artery stenosis**, which limits renal perfusion and leads to activation of the renin-angiotensin-aldosterone system. The resultant **hypertension** is often the earliest sign of the disease. Other presentations are related to locations of the dysplastic artery; **cerebrovascular involvement** (ie, headache, stroke, aneurysm rupture), mesenteric ischemia, or extremity claudication may be seen.

(Choices A and B) Adrenal tumors that can present with severe hypertension include pheochromocytoma and

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(Choices A and B) Adrenal tumors that can present with severe hypertension include pheochromocytoma and aldosterone- or cortisol-secreting adrenocortical adenomas. Coarctation of the aorta also causes hypertension, with blood pressure higher in the upper versus lower extremities. Due to the elevated blood pressure, these diseases can cause headaches and intraparenchymal hemorrhage in predisposed individuals, but they are not associated with fibrotic webbing or aneurysm formation.

(Choice C) Hypertrophic cardiomyopathy may present with sudden death in young patients due to left ventricular outflow obstruction; histology demonstrates hypertrophied myocytes and interstitial fibrosis. However, hypertrophic cardiomyopathy is not associated with aneurysm formation.

(Choice E) Thyroid follicular hyperplasia can cause hyperthyroidism (eg, Graves disease, thyroid adenoma). This commonly causes tachycardia, tremor, and palpitations but would not cause aneurysm formation.

Educational objective:
Fibromuscular dysplasia is characterized by abnormal tissue growth within arterial walls, resulting in stenotic and

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disease.

FMD can involve any artery but most commonly the renal, cerebral (eg, carotid, vertebral), and visceral arteries. Up to 80% of patients develop **renal artery stenosis**, which limits renal perfusion and leads to activation of the renin-angiotensin-aldosterone system. The resultant **hypertension** is often the earliest sign of the disease. Other presentations are related to locations of the dysplastic artery; **cerebrovascular involvement** (ie, headache, stroke, aneurysm rupture), mesenteric ischemia, or extremity claudication may be seen.

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Educational objective:
Fibromuscular dysplasia is characterized by abnormal tissue growth within arterial walls, resulting in stenotic and tortuous arteries that can cause tissue ischemia and are prone to aneurysm formation. Pathology typically demonstrates alternating fibromuscular webs and aneurysmal dilation with absent internal elastic lamina (string-of-beads appearance). Renovascular hypertension occurs due to renal artery stenosis and activation of the renin-angiotensin-aldosterone system.

Pathology	Renal, Urinary Systems & Electrolytes	Renal artery stenosis

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A 54-year-old man comes to the hospital due to acute-onset right flank pain associated with nausea. Five years ago, the patient had nephrolithiasis; the renal calculi passed spontaneously with intravenous fluids. Review of systems is positive for occasional palpitations. Other medical problems include hypertension, obesity, and obstructive sleep apnea. Temperature is 38 C (100.4 F), blood pressure is 170/98 mm Hg, pulse is 90/min, and respirations are 18/min. Cardiopulmonary examination shows no abnormalities. Right flank tenderness is present. Urinalysis demonstrates 2+ red blood cells and no white blood cells or protein. A representative kidney specimen is shown below:



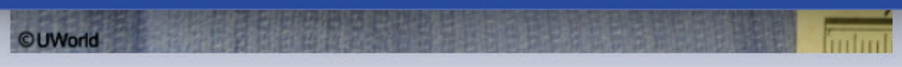
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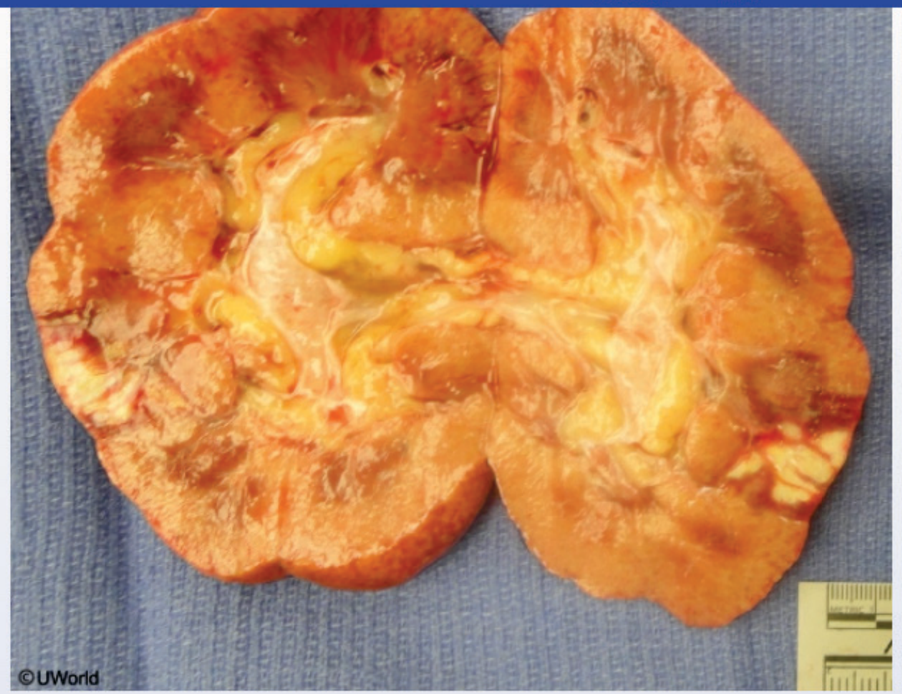
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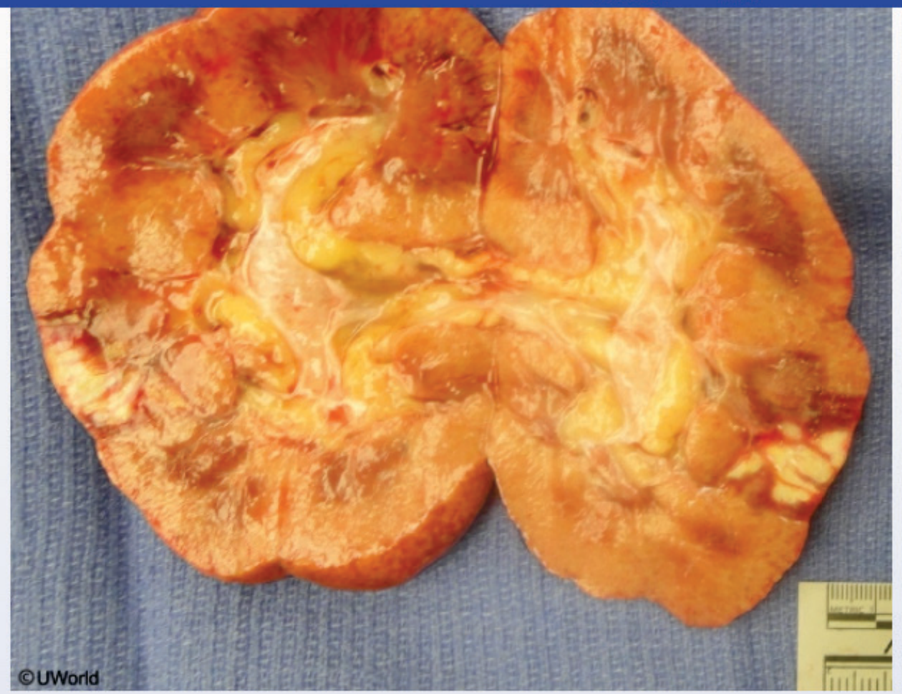


Which of the following is the most likely diagnosis?

- A. Nephrolithiasis
- B. Pyelonephritis
- C. Renal cell carcinoma
- D. Renal infarction
- E. Renal papillary necrosis

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Which of the following is the most likely diagnosis?

- A. Nephrolithiasis (5%)
- ✗ B. Pyelonephritis (9%)
- C. Renal cell carcinoma (11%)
- ✓ D. Renal infarction (56%)
- E. Renal papillary necrosis (17%)

Incorrect
Correct answer
D

56%
Answered correctly

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Time Spent

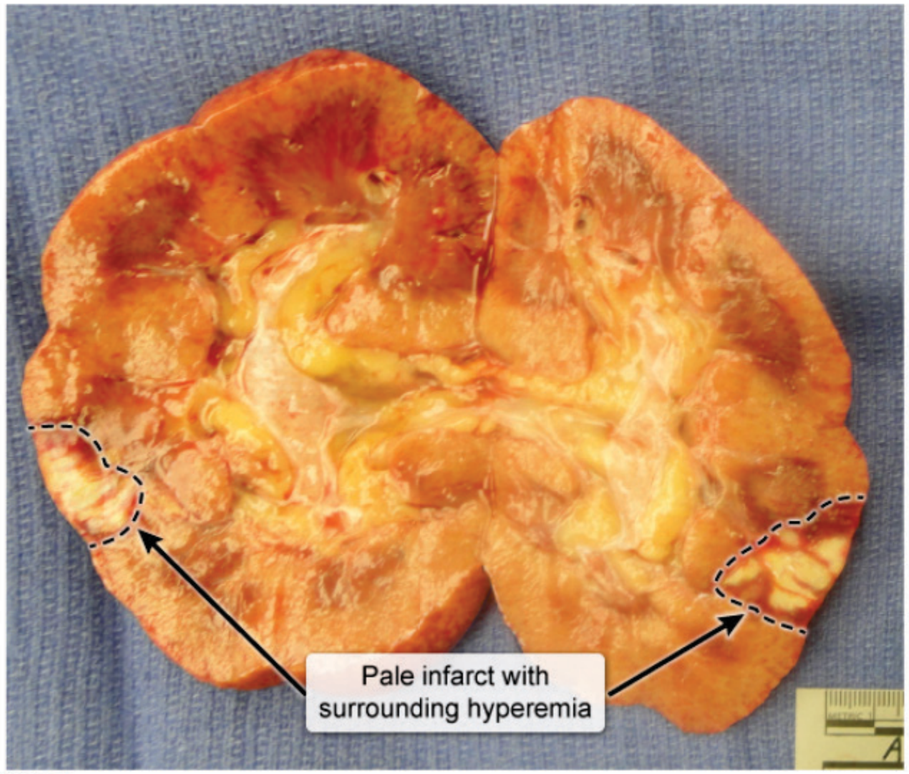
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E. Renal papillary necrosis (17%)

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Renal infarction



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surrounding hyperemia

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This patient with flank pain, low-grade fever, and hematuria has a **renal infarction**. Renal infarctions are most commonly caused by **cardioembolic disease** (ie, originating from the left atrium or ventricle). **Atrial fibrillation**, suggested by this patient's intermittent palpitations and history of sleep apnea, is the greatest risk factor, although emboli from mural thrombi (following myocardial infarction), prosthetic valves, or valvular vegetations (ie, endocarditis) are also implicated. Complete occlusion of the renal artery can occur more rarely due to direct arterial injury (eg, dissection, vasculitis) or hypercoagulable states (eg, antiphospholipid syndrome). The kidneys are predisposed to embolic infarctions due to their high perfusion rates and limited collateral circulation.

Typical presenting symptoms include **flank pain**, **nausea**, vomiting, and low-grade fever. **Hypertension** can occur due to renin release from hypoxic renal tissue. Common laboratory abnormalities include elevated lactate dehydrogenase (suggesting cell necrosis), hematuria, and mild leukocytosis; however, serum creatinine is often normal unless bilateral or massive unilateral disease is present. Gross pathology shows sharply demarcated, yellow-white, **wedge-shaped infarcts** surrounded by hyperemic tissue.

(Choice A) Nephrolithiasis can cause flank pain and hematuria, but renal injury is typically due to obstruction, causing hydronephrosis. Renal calyces and ureters are dilated, and infarctions do not occur.

(Choice B) Pyelonephritis can also cause flank pain and nausea, and focal abscesses are usually present. However, pyuria is expected on urinalysis and patients typically have dysuria.

(Choice C) Renal cell carcinoma can cause flank pain and hematuria, but gross pathology demonstrates yellow, well-circumscribed lesions with areas of focal hemorrhage.

(Choice E) Papillary necrosis, often caused by excessive chronic analgesic use, demonstrates cortical atrophy with necrotic, sloughing papillae. Focal, wedge-shaped necrosis is not seen.

Educational objective:
Renal infarctions are most commonly caused by cardioembolic disease; atrial fibrillation is the greatest risk factor. Clinical features include flank pain, nausea, vomiting, low-grade fever, and hypertension (due to renin release from

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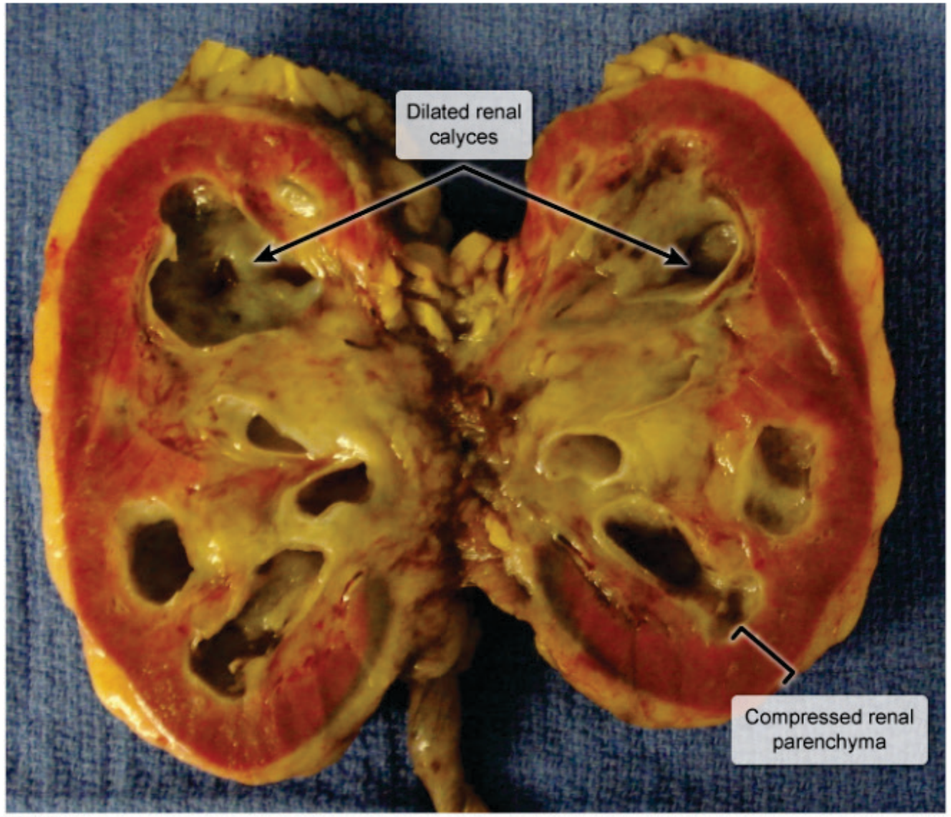
Educational objective:
Renal infarctions are most commonly caused by cardioembolic disease; atrial fibrillation is the greatest risk factor. Clinical features include flank pain, nausea, vomiting, low-grade fever, and hypertension (due to renin release from hypoxic tissue). Gross pathology demonstrates sharply demarcated, yellow-white, wedge-shaped areas with surrounding hyperemia.

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arterial injury (eg, dissection, vasculitis) or hypercoagulable states (eg, antiphospholipid syndrome). The kidneys

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Hydronephrosis

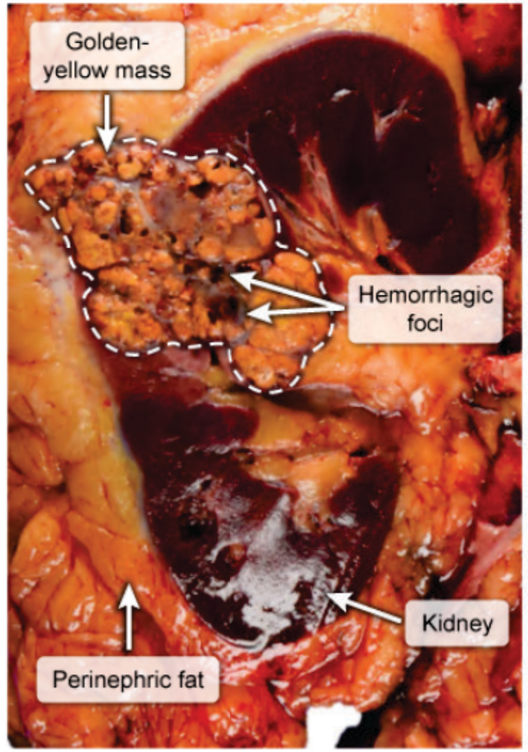


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arterial injury (eg, dissection, vasculitis) or hypercoagulable states (eg, antiphospholipid syndrome). The kidneys

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Clear cell renal cell carcinoma



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Subject System Topic

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A 56-year-old man with chronic kidney disease is seen for a routine follow-up visit. The patient also has type 2 diabetes, hypertension, and hyperlipidemia. His serum creatinine level has been increasing over the past 2 years. Blood pressure is 144/90 mm Hg and pulse is 88/min. Weight is 80 kg (176 lb). Physical examination is normal except for trace pitting ankle edema. Serum creatinine level is 1.8 mg/dL; 1 year ago, serum creatinine was 1.4 mg/dL. Serum calcium and phosphorus levels are in the normal range. Which of the following is most likely responsible for maintaining the serum phosphorus within normal range despite declining renal function?

- A. Elevated serum thyrotropin
- B. Hypocalcemia
- C. Hypomagnesemia
- D. Increased serum fibroblast growth factor 23 level
- E. Suppressed serum parathyroid hormone level

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- A. Elevated serum thyrotropin (2%)
- ✗ B. Hypocalcemia (13%)
- C. Hypomagnesemia (13%)
- ✓ D. Increased serum fibroblast growth factor 23 level (40%)
- E. Suppressed serum parathyroid hormone level (29%)

Incorrect
Correct answer
D

40%
Answered correctly

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Explanation

Fibroblast growth factor 23 & phosphate metabolism	
Secretion	• Produced by osteocytes • Production increased by hyperphosphatemia, 1,25-dihydroxyvitamin D

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Explanation

Fibroblast growth factor 23 & phosphate metabolism	
Secretion	• Produced by osteocytes • Production increased by hyperphosphatemia, 1,25-dihydroxyvitamin D
Metabolic effects	• Inhibits synthesis of 1,25-dihydroxyvitamin D ◦ ↓ intestinal phosphate absorption ◦ ↓ renal phosphate reabsorption • Suppresses renal sodium/phosphate cotransporter IIa ◦ ↓ renal phosphate reabsorption

Renal clearance of phosphate depends on adequate filtration of phosphate in the glomerulus. Patients with chronic kidney disease (CKD) and decreased glomerular filtration can experience inadequate phosphate excretion leading to hyperphosphatemia.

Fibroblast growth factor 23 (FGF23) is secreted by osteocytes in response to hyperphosphatemia and binds the FGF23 receptor along with the coreceptor Klotho. In the kidneys, FGF23 **suppresses 1-hydroxylase** (which converts 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, the more active form), leading to reduced levels of 1,25-dihydroxyvitamin D. This causes **decreased intestinal phosphate absorption** and **decreased renal phosphate reabsorption**. Concurrently, FGF23 **downregulates sodium/phosphate cotransporter IIa** in the renal tubules, leading to an additional decrease in phosphate reabsorption. The net effect is greater elimination of phosphate in the urine and feces.

FGF23 is one of the earliest counterregulatory factors in responding to hyperphosphatemia, and it may be elevated

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Renal clearance of phosphate depends on adequate filtration of phosphate in the glomerulus. Patients with chronic kidney disease (CKD) and decreased glomerular filtration can experience inadequate phosphate excretion leading to hyperphosphatemia.

Fibroblast growth factor 23 (FGF23) is secreted by osteocytes in response to hyperphosphatemia and binds the FGF23 receptor along with the coreceptor Klotho. In the kidneys, FGF23 **suppresses 1-hydroxylase** (which converts 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, the more active form), leading to reduced levels of 1,25-dihydroxyvitamin D. This causes **decreased intestinal phosphate absorption** and **decreased renal phosphate reabsorption**. Concurrently, FGF23 **downregulates sodium/phosphate cotransporter IIa** in the renal tubules, leading to an additional decrease in phosphate reabsorption. The net effect is greater elimination of phosphate in the urine and feces.

FGF23 is one of the earliest counterregulatory factors in responding to hyperphosphatemia, and it may be elevated even before circulating phosphate levels are above laboratory reference ranges. Serum FGF23 levels are useful as an **early marker** for monitoring abnormal phosphate metabolism in patients with CKD.

(Choice A) In contrast to the parathyroid glands, which have a significant role in calcium and phosphate homeostasis, the pituitary-thyroid axis (ie, thyrotropin, thyroid hormone) is not a major regulator of calcium and phosphate metabolism.

(Choices B and E) Hypocalcemia and hyperphosphatemia in CKD induce secretion (not suppression) of parathyroid hormone (PTH) from the parathyroid glands. PTH causes release of calcium from bone, renal calcium retention, and increased renal phosphate excretion. Despite rising PTH levels in CKD (ie, secondary hyperparathyroidism), patients tend to develop hyperphosphatemia due to the declining glomerular filtration rate (reduces filtered phosphate load).

(Choice C) As with phosphate, declining glomerular filtration generally leads to magnesium retention, not wasting. Moreover, clinically significant alterations in magnesium levels are typically seen only in patients with advanced CKD (ie, glomerular filtration rate <10-30 mL/min; serum creatinine >2-3 mg/dL).

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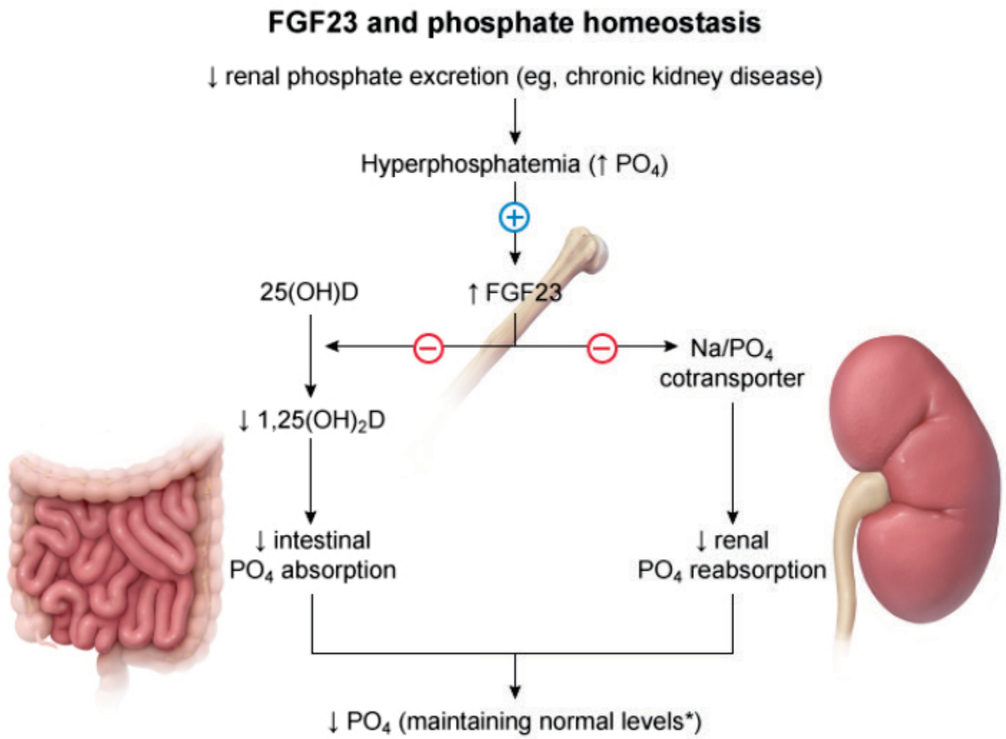
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Educational objective:
Patients with chronic kidney disease (CKD) can develop hyperphosphatemia due to decreased filtration of phosphate. Fibroblast growth factor 23 (FGF23) is secreted in response to hyperphosphatemia and lowers plasma phosphate by reducing intestinal absorption and renal reabsorption of phosphate. FGF23 levels are useful as an early marker of abnormal phosphate metabolism in patients with CKD.

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- Inhibits synthesis of 1,25-dihydroxyvitamin D

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*Compensatory response declines as chronic kidney disease progresses, leading to loss of homeostasis

25(OH)D = 25-hydroxyvitamin D; **$1,25(OH)_2D$** = 1,25-dihydroxyvitamin D; **FGF23** = fibroblast growth factor 23.

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(Choices B and E) Hypocalcemia and hyperphosphatemia in CKD induce secretion (not suppression) of parathyroid hormone (PTH) from the parathyroid glands. PTH causes release of calcium from bone, renal calcium

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A 17-year-old boy is brought to the office due to occasional blood in the urine. The first episode occurred 1 year ago during a flulike illness, and resolved spontaneously. The patient had a similar episode about 6 months ago, which also seemed to resolve. He has no other medical conditions and does not use tobacco or alcohol. There is no history of blood or kidney disorders in the family. Vital signs are normal. On laboratory evaluation, blood urea nitrogen level is 14 mg/dL and creatinine is 0.8 mg/dL. Urinalysis results are as follows:

Specific gravity	1.013
Protein	+2
Blood	trace
Glucose	negative
Ketones	negative
Leukocyte esterase	negative
Nitrites	negative
White blood cells	1-2/hpf
Red blood cells	20-30/hpf

A renal biopsy is performed. Which of the following findings is most likely to be seen on microscopic evaluation?

- A. Apple-green birefringent mesangial deposits
- B. Crescent formation with linear IgG deposits
- C. Effacement of podocyte foot processes
- D. Granular IgG and C3 deposits

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Specific gravity	1.013
Protein	+2
Blood	trace
Glucose	negative
Ketones	negative
Leukocyte esterase	negative
Nitrites	negative
White blood cells	1-2/hpf
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- A. Apple-green birefringent mesangial deposits
- B. Crescent formation with linear IgG deposits
- C. Effacement of podocyte foot processes
- D. Granular IgG and C3 deposits
- E. Lamellated basement membrane
- F. Mesangial deposition of IgA
- G. Sclerosis of a portion of some glomeruli
- H. Thin basement membrane

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Specific gravity	1.013
Protein	+2
Blood	trace
Glucose	negative
Ketones	negative
Leukocyte esterase	negative
Nitrites	negative
White blood cells	1-2/hpf
Red blood cells	20-30/hpf

A renal biopsy is performed. Which of the following findings is most likely to be seen on microscopic evaluation?

- A. Apple-green birefringent mesangial deposits (1%)
- B. Crescent formation with linear IgG deposits (4%)
- ✗ C. Effacement of podocyte foot processes (9%)
- D. Granular IgG and C3 deposits (23%)
- E. Lamellated basement membrane (1%)
- ✓ F. Mesangial deposition of IgA (57%)
- G. Sclerosis of a portion of some glomeruli (1%)
- H. Thin basement membrane (2%)

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Pathologic findings in nephritic syndrome		
	Cause of glomerular injury	**Characteristic biopsy features**
Poststreptococcal glomerulonephritis	Antibodies against streptococcal antigens that deposit in GBM	• IF: C3 granular staining along GBM • EM: subepithelial humps
Anti-GBM disease	Antibodies against type IV collagen in GBM	• LM: glomerular crescents • IF: linear staining (IgG) along GBM
Rapidly progressive glomerulonephritis	Severe immunologic injury (eg, anti-GBM antibodies, immune complex deposition)	• LM: glomerular crescents • IF: fibrin in crescents
IgA nephropathy	Deposition of IgA-containing complexes	• LM: mesangial hypercellularity • IF: IgA in mesangium
Alport syndrome	Defective type IV collagen in GBM	• EM: lamellated appearance of GBM
EM = electron microscopy; **GBM** = glomerular basement membrane; **IF** = immunofluorescence; **LM** = light microscopy.		

This patient likely has **IgA nephropathy** (Berger disease), the most common cause of glomerulonephritis. It typically affects older children and young adults and presents with **painless hematuria** that is often **accompanied by** an **upper respiratory tract infection**. The hematuria lasts for several days and then subsides temporarily, returning every few months or with another upper respiratory infection (synpharyngitic hematuria). Complement levels are usually normal. Renal biopsy will show mesangial hypercellularity with mesangial IgA deposits seen by immunofluorescence.

When IgA nephropathy is accompanied by extrarenal symptoms (eg, abdominal pain, arthralgias, purpuric skin lesions), the syndrome is called Henoch-Schönlein purpura.

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When IgA nephropathy is accompanied by extrarenal symptoms (eg, abdominal pain, arthralgias, purpuric skin lesions), the syndrome is called Henoch-Schönlein purpura.

(Choice A) The kidney is often affected by amyloidosis. On Congo red staining, amyloid deposits appear red-pink under light microscopy and have an apple-green birefringence under polarized light. Amyloidosis typically presents in older adults as nephrotic syndrome with significant edema and proteinuria.

(Choice B) Crescent formation with linear IgG deposits occurs in patients with anti-glomerular basement membrane antibody disease (Goodpasture disease). This condition generally presents as rapidly progressive glomerulonephritis associated with an acute rise in creatinine and decreased urine output; patients also often have hemoptysis. The disease is rare in children.

(Choice C) Minimal change disease (MCD) is characterized by effacement of podocyte foot processes on electron microscopy. MCD typically results in nephrotic syndrome with generalized edema and high levels of proteinuria; recurrent hematuria associated with an upper respiratory infection is more consistent with IgA nephropathy.

(Choice D) Poststreptococcal glomerulonephritis (PSGN) demonstrates granular IgG and C3 deposits along the glomerular basement membrane. However, hematuria in PSGN usually develops 1-3 weeks after streptococcal pharyngitis (postpharyngitic nephritis), and reoccurrence is rare.

(Choice E) Alport syndrome is a disorder of type IV collagen that causes a nephritic syndrome; however, it is associated with hearing loss and ocular abnormalities. Electron microscopy shows a lamellated basement membrane with irregular thinning and thickening ("basket-weave" appearance).

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(Choice E) Alport syndrome is a disorder of type IV collagen that causes a nephritic syndrome; however, it is associated with hearing loss and ocular abnormalities. Electron microscopy shows a lamellated basement membrane with irregular thinning and thickening ("basket-weave" appearance).

(Choice G) Focal segmental glomerular sclerosis typically causes nephrotic syndrome. Recurrent episodes of macroscopic hematuria are unexpected.

(Choice H) Thin basement membrane disease is an autosomal dominant disorder that results in a thin basement membrane with recurrent microscopic hematuria, gross hematuria, or flank pain. Due to the inheritance pattern, patients typically have a family history of hematuria.

Educational objective:
IgA nephropathy (Berger disease) frequently presents as recurrent, self-limited, painless hematuria; episodes often occur concurrently with an upper respiratory tract infection. Kidney biopsy will show mesangial IgA deposits on immunofluorescence. In contrast, poststreptococcal glomerulonephritis is seen 1-3 weeks after streptococcal pharyngitis and is usually not recurrent.

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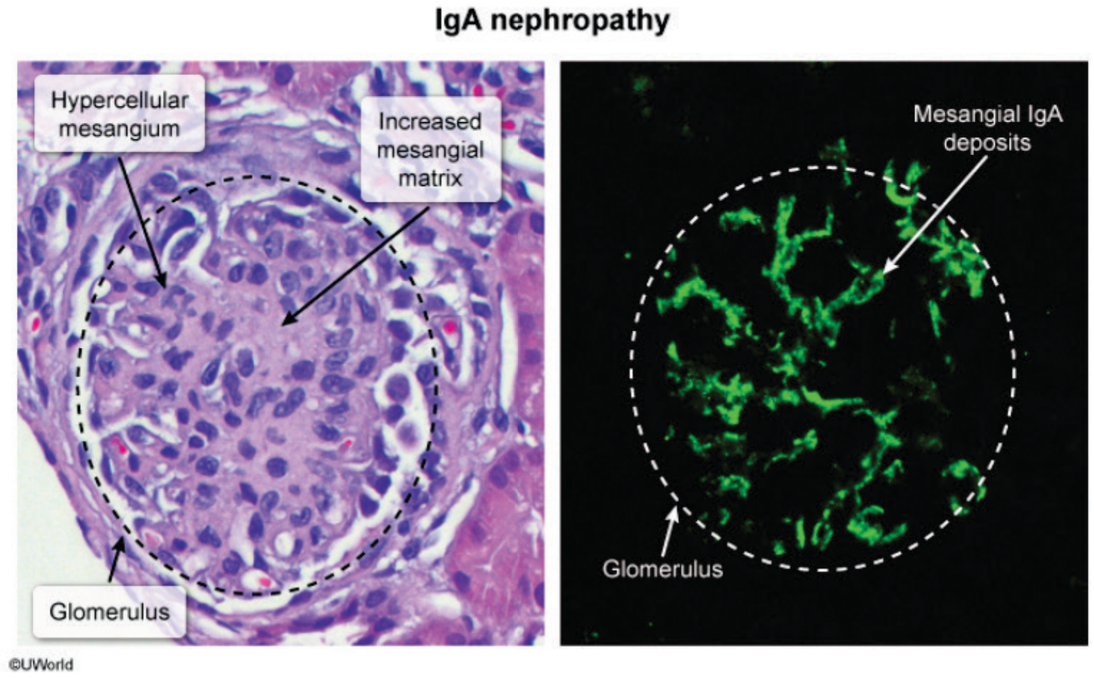
Nephritic vs nephrotic syndrome		
	Nephritic	**Nephrotic**
Proteinuria	Mild	Significant (>3.5 g/day)
Serum albumin	Normal	Decreased
Edema	Mild	Significant
GFR	Decreased	Normal
Hypertension	Yes	No
Hematuria	Yes	No
Pyuria	Yes	No
Casts	RBC	Fatty or none
GFR = glomerular filtration rate; **RBC** = red blood cell.		

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recurrent hematuria associated with an upper respiratory infection is more consistent with IgA nephropathy.

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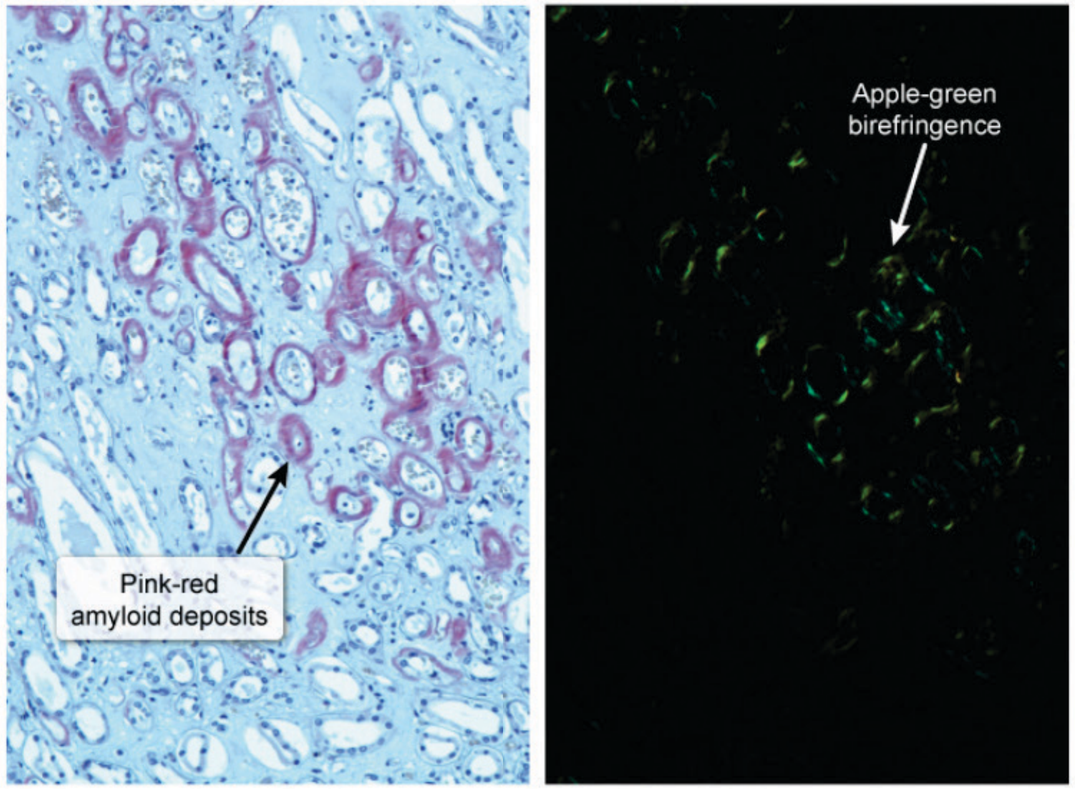
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recurrent hematuria associated with an upper respiratory infection is more consistent with IgA nephropathy.

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Renal amyloidosis



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Congo red stain

Congo red stain under polarized light

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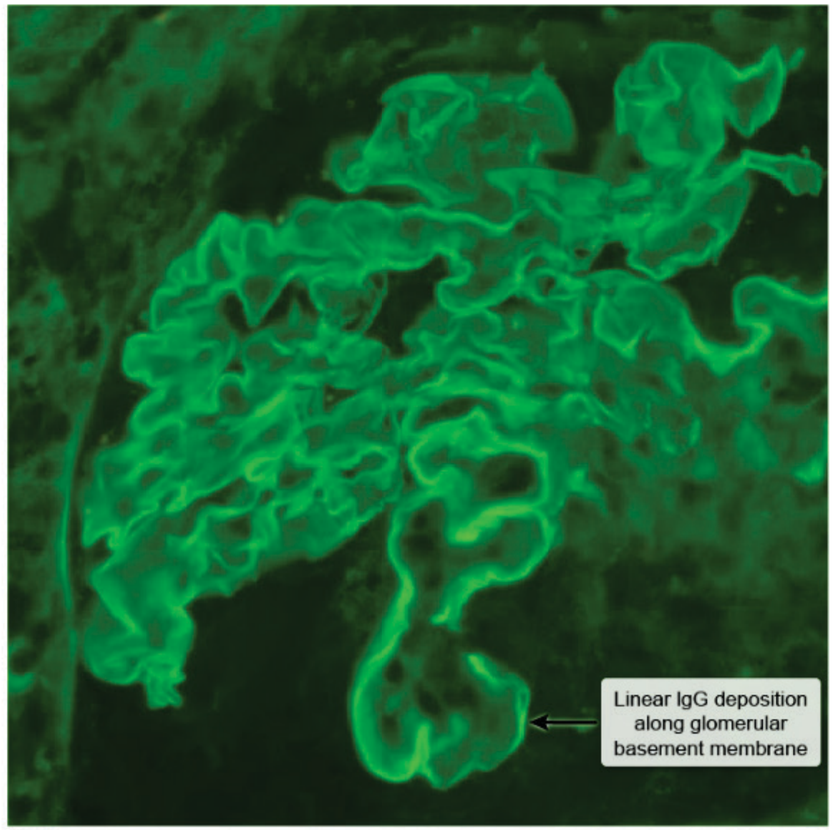
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Anti-glomerular basement membrane disease



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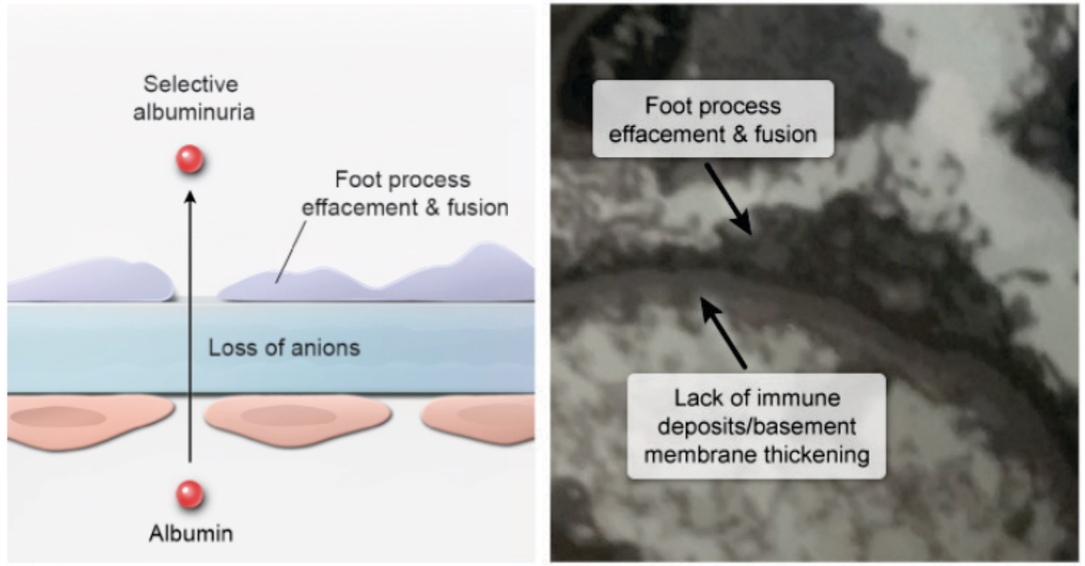
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membrane with irregular thinning and thickening ("basket-weave" appearance).

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Minimal change disease



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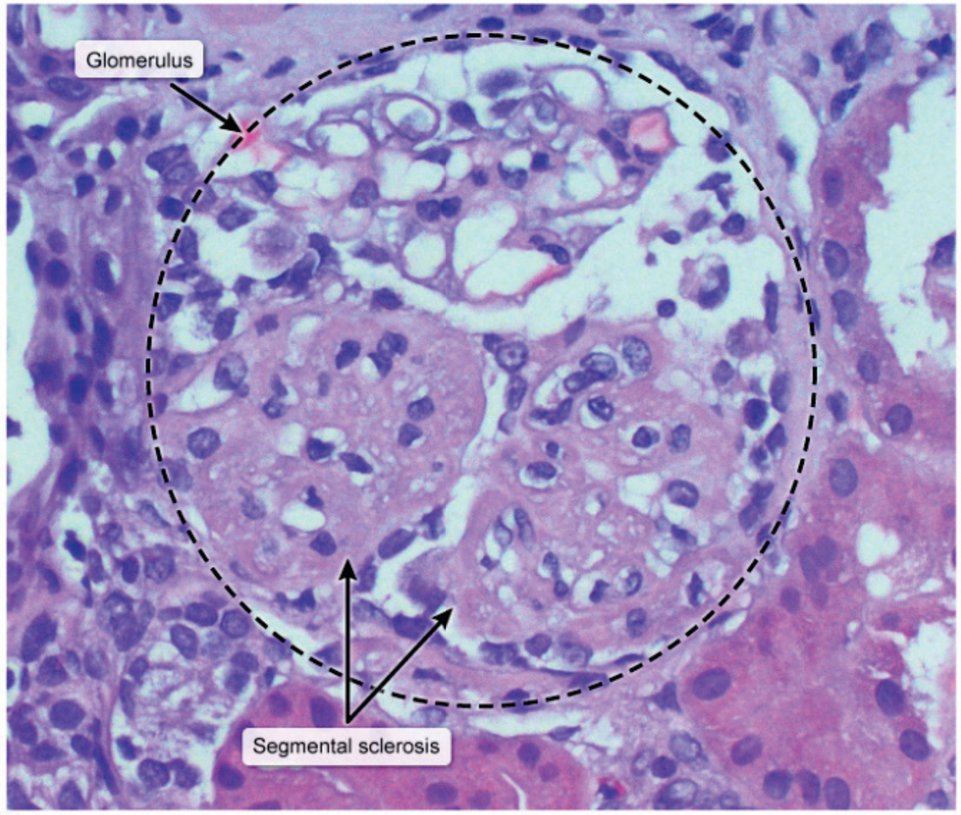
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under light microscopy and have an apple-green birefringence under polarized light. Amyloidosis typically presents

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Focal segmental glomerulosclerosis



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occur concurrently with an upper respiratory tract infection. Kidney biopsy will show mesangial IgA deposits on

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A 34-year-old woman comes to the office due to a 3-day history of watery diarrhea. The patient has no fever. She has no other medical conditions and takes no medications. Blood pressure is 120/80 mm Hg and pulse is 90/min. Examination shows mild abdominal discomfort but is otherwise normal. Compared to normal laboratory values, which of the following findings are most likely present in this patient?

	Blood pH	$PaCO_2$	Serum bicarbonate
A.	Low	Low	Low
B.	Low	High	Normal
C.	Low	High	High
D.	High	Low	Low
E.	High	High	High

Submit

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	Blood pH	$PaCO_2$	Serum bicarbonate	
✓ A.	Low	Low	Low	(74%)
✗ B.	Low	High	Normal	(3%)
C.	Low	High	High	(2%)
D.	High	Low	Low	(7%)
E.	High	High	High	(11%)

Incorrect
Correct answer
A

74%
Answered correctly

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Explanation

Common causes of primary acid-base disturbance	
	Elevated anion gap • Poor tissue perfusion (ie, lactic acidosis) • Diabetic ketoacidosis

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Common causes of primary acid-base disturbance	
Metabolic acidosis	**Elevated anion gap** • Poor tissue perfusion (ie, lactic acidosis) • Diabetic ketoacidosis • Renal failure (ie, uremia) • Certain toxicities (eg, methanol, ethylene glycol) **Normal anion gap** • Severe diarrhea • Renal tubular acidosis • Excess normal saline infusion
Metabolic alkalosis	• Nasogastric suctioning or severe vomiting • Diuretic overuse • Primary hyperaldosteronism
Respiratory acidosis (hypoventilation)	• Central respiratory depression (eg, opioid overdose) • OHS, neuromuscular weakness • Chronic obstructive pulmonary disease
Respiratory alkalosis (hyperventilation)	• Acute V/Q mismatch (eg, PE, pneumonia) • Anxiety, inadequate pain control • High altitude, pregnancy
OHS = obesity hypoventilation syndrome; **PE** = pulmonary embolism; **V/Q** = ventilation/perfusion.	

This patient with several days of **diarrhea** is expected to have **primary metabolic acidosis**, with low blood pH (<7.35), low serum bicarbonate (HCO_3^-) (<24 mEq/L), and compensatory low partial pressure of carbon dioxide in arterial blood ($PaCO_2$) (<40 mm Hg). Severe diarrhea involves substantial **loss of HCO_3^-** in the stool, leading to

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(hyperventilation)	• High altitude, pregnancy
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(Choices B and C) Low pH with high $PaCO_2$ is consistent with respiratory acidosis. Full metabolic compensation via HCO_3^- reabsorption by the kidneys requires approximately 72 hours; therefore, HCO_3^- is high in chronic respiratory acidosis (eg, CO_2 retention due to chronic obstructive pulmonary disease) and near normal in acute respiratory acidosis (eg, suppressed respiratory drive due to opioid overdose).

(Choice D) High pH with low $PaCO_2$ represents respiratory alkalosis, as occurs with hyperventilation at high altitude. HCO_3^- is low due to compensatory metabolic acidosis.

(Choice E) High pH with high HCO_3^- represents metabolic alkalosis, as occurs with the loss of H^+ with severe vomiting. $PaCO_2$ is high due to compensatory respiratory acidosis.

Educational objective:
Severe diarrhea causes substantial loss of bicarbonate (HCO_3^-) in the stool and is a common cause of nonanion gap metabolic acidosis. Low blood pH (<7.35) and low serum HCO_3^- (<24 mEq/L) are expected with compensatory low arterial partial pressure of carbon dioxide ($PaCO_2$) (compensatory respiratory alkalosis).

Physiology	Renal, Urinary Systems & Electrolytes	Metabolic acidosis
Subject	System	Topic

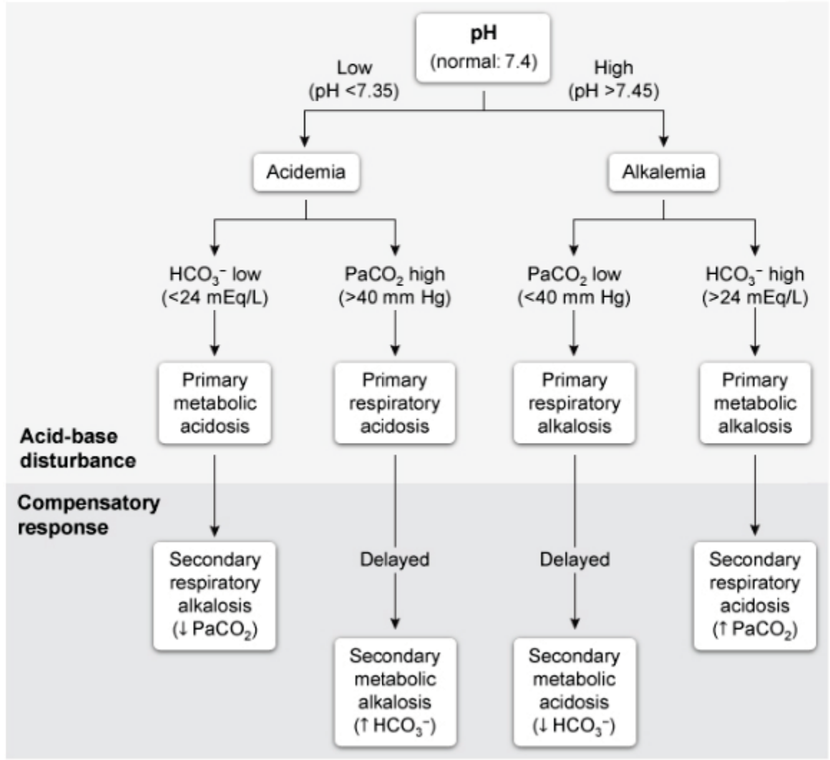
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(hyperventilation)	• High altitude, pregnancy

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Arterial blood gas interpretation of acid-base disorders



* The normal ranges for $PaCO_2$ and HCO_3^- vary slightly around 40 mm Hg and 24 mEq/L.
For simplicity, these numbers should be used as a normal baseline for acid-base calculations.

HCO_3^- = bicarbonate; **$PaCO_2$** = partial pressure of carbon dioxide in arterial blood.

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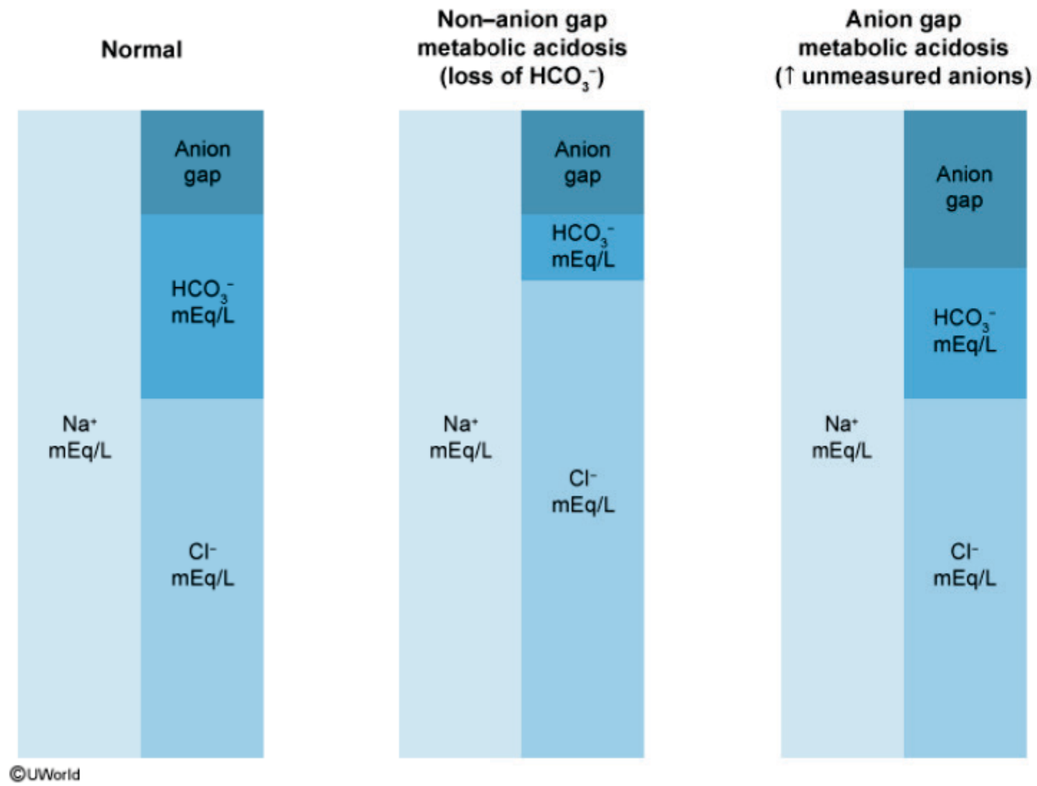
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(Hyperventilation)	• High altitude, pregnancy

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A 7-month-old girl is brought to the office due to poor weight gain over the past several months. Her mother says that her day care has noticed she has many more wet diapers than other infants in her class. The patient's weight has decreased from the 50th percentile at age 2 months to the 3rd percentile today, and physical examination shows widening of her wrist joints. Following serum and urine laboratory studies, she is diagnosed with a condition characterized by defective reabsorption of bicarbonate (HCO_3^-) in the proximal convoluted tubule. In addition to decreased serum HCO_3^-, which of the following sets of laboratory results are most likely present in this patient?

	Serum chloride	Serum glucose	Serum phosphorus
◯ A.	Decreased	Increased	Normal
◯ B.	Decreased	Normal	Decreased
◯ C.	Increased	Increased	Decreased
◯ D.	Increased	Normal	Decreased
◯ E.	Normal	Increased	Normal
◯ F.	Normal	Normal	Normal

Submit

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	Serum chloride	Serum glucose	Serum phosphorus	
○ A.	Decreased	Increased	Normal	(5%)
✗ ◉ B.	Decreased	Normal	Decreased	(29%)
○ C.	Increased	Increased	Decreased	(12%)
✓ ○ D.	Increased	Normal	Decreased	(40%)
○ E.	Normal	Increased	Normal	(2%)
○ F.	Normal	Normal	Normal	(6%)

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Correct answer
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40%
Answered correctly

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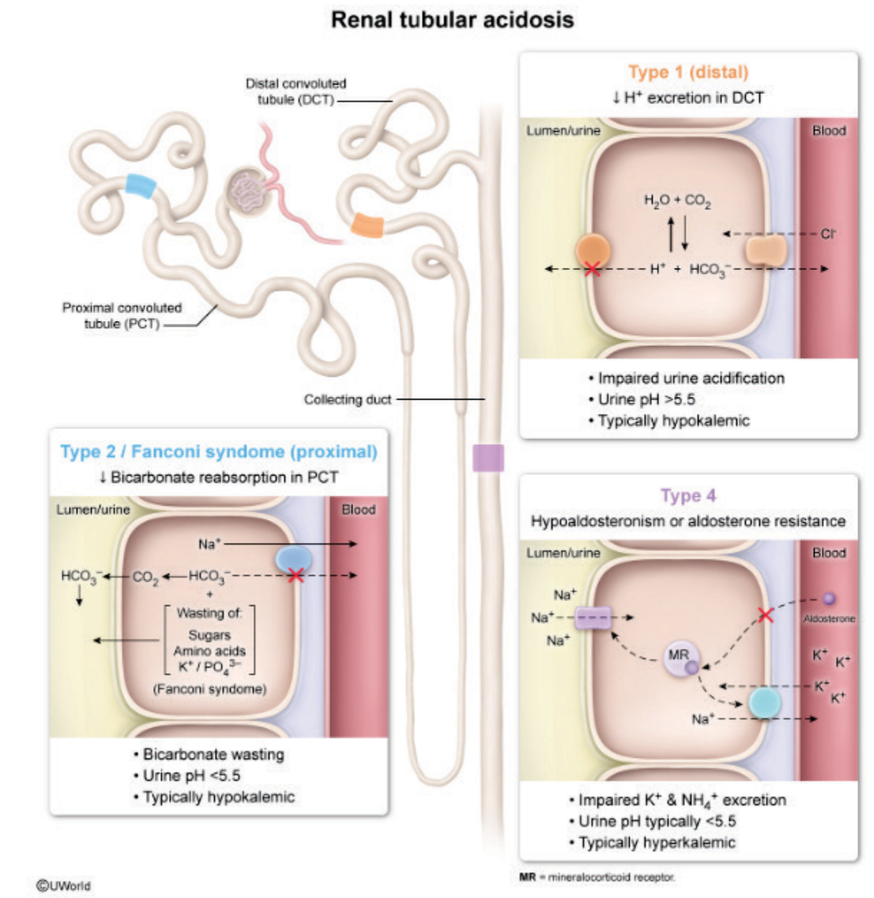
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Explanation

Renal tubular acidosis

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• Urine pH <5.5
• Typically hypokalemic
• Impaired K+ & NH4+ excretion

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MR = mineralocorticoid receptor.

This patient cannot reabsorb bicarbonate (HCO_3^-) in the **proximal convoluted tubule** (PCT), which is characteristic of type 2 renal tubular acidosis (RTA). **Type 2 RTA** commonly occurs as part of a generalized resorptive dysfunction affecting proximal tubular cells (ie, **Fanconi syndrome**). Patients presenting in infancy or childhood often have an underlying genetic condition (eg, cystinosis, galactosemia, Dent disease) that predisposes to tubular dysfunction.

The PCT is normally responsible for **reabsorbing HCO_3^-** as well as **glucose**, **phosphate**, **potassium**, water, and amino acids. The proximal tubule damage that occurs in Fanconi syndrome leads to loss of these substances in the urine, producing the following clinical effects:

- Inability to resorb HCO_3^- results in a normal anion gap **metabolic acidosis**. The resulting decrease in serum HCO_3^- is compensated by **increased serum chloride** (Cl^-) to maintain electronegative balance.
- Excessive tubular glucose impairs renal concentrating ability by acting as an osmotic diuretic, contributing to development of **polyuria** (eg, more wet diapers) and episodes of hypovolemia . However, plasma glucose is tightly regulated by mechanisms (eg, insulin, glucagon) independent of renal reabsorption. Therefore, serum **glucose remains normal**.
- **Hypophosphatemia** leads to rickets (eg, widening of wrist joints, frontal bossing, bowing of the legs).
- **Hypokalemia** can cause muscle weakness.
- Loss of amino acids and low-molecular-weight proteins does not typically have a significant effect, but aminoaciduria can be a general marker of proximal tubular dysfunction.

Chronic acidosis, hypophosphatemia, and hypokalemia also contribute to **growth failure**, as seen in this patient.

Educational objective:
The proximal convoluted tubule (PCT) is responsible for reabsorption of bicarbonate as well as glucose,

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The PCT is normally responsible for **reabsorbing HCO_3^-** as well as **glucose**, **phosphate**, **potassium**, water, and amino acids. The proximal tubule damage that occurs in Fanconi syndrome leads to loss of these substances in the urine, producing the following clinical effects:

- Inability to resorb HCO_3^- results in a normal anion gap **metabolic acidosis**. The resulting decrease in serum HCO_3^- is compensated by **increased serum chloride** (Cl^-) to maintain electronegative balance.
- Excessive tubular glucose impairs renal concentrating ability by acting as an osmotic diuretic, contributing to development of **polyuria** (eg, more wet diapers) and episodes of hypovolemia . However, plasma glucose is tightly regulated by mechanisms (eg, insulin, glucagon) independent of renal reabsorption. Therefore, serum **glucose remains normal**.
- **Hypophosphatemia** leads to rickets (eg, widening of wrist joints, frontal bossing, bowing of the legs).
- **Hypokalemia** can cause muscle weakness.
- Loss of amino acids and low-molecular-weight proteins does not typically have a significant effect, but aminoaciduria can be a general marker of proximal tubular dysfunction.

Chronic acidosis, hypophosphatemia, and hypokalemia also contribute to **growth failure**, as seen in this patient.

Educational objective:
The proximal convoluted tubule (PCT) is responsible for reabsorption of bicarbonate as well as glucose, phosphate, potassium, water, and amino acids. Generalized PCT dysfunction (eg, Fanconi syndrome) results in urinary loss of these substances; in addition, serum chloride rises to maintain electronegative balance from bicarbonate loss and serum glucose remains normal due to intact counterregulatory mechanisms.

Pathophysiology	Renal, Urinary Systems & Electrolytes	Renal tubular acidosis
Subject	System	Topic

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resorptive dysfunction affecting proximal tubular cells (ie, **Fanconi syndrome**). Patients presenting in infancy or
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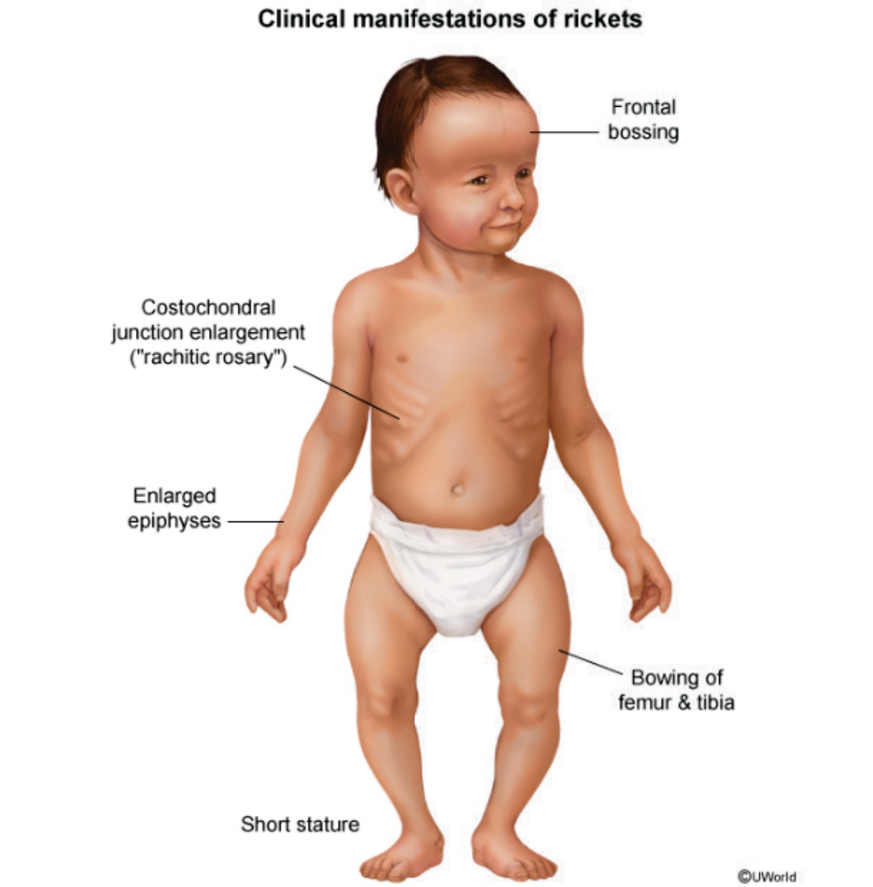
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bicarbonate loss and serum glucose remains normal due to intact counterregulatory mechanisms.

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A 75-year-old man comes to the office for follow-up of hypertension. In recent weeks, his blood pressure has consistently been 160-165/85-90 mm Hg. Medical history includes a right carotid endarterectomy for recurrent transient ischemic attacks, a myocardial infarction 2 years ago, and coronary artery bypass surgery for unstable angina 1 year ago. The patient currently takes metoprolol, clopidogrel, amlodipine, and rosuvastatin. He quit smoking 20 years ago and does not drink alcohol. The patient is compliant with his medical therapy and office visits. Ramipril is added to his medication regimen. One week later, creatinine is 2.1 mg/dL, up from a baseline of 1.1 mg/dL. Assuming the patient's baseline urinalysis is normal, a repeat urinalysis at this time would most likely reveal which of the following?

	Protein	Red blood cells	White blood cells	Casts	Other findings
○ A.	2+	50	10	RBC	none
○ B.	1+	0-1	50	WBC	eosinophils
○ C.	-	50	0-1	none	needle-shaped crystals
○ D.	4+	0-1	0-1	none	oval fat bodies
○ E.	-	0-1	0-1	none	none

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	Protein	Red blood cells	White blood cells	Casts	Other findings	
A.	2+	50	10	RBC	none	(11%)
✗ B.	1+	0-1	50	WBC	eosinophils	(9%)
C.	-	50	0-1	none	needle-shaped crystals	(2%)
D.	4+	0-1	0-1	none	oval fat bodies	(8%)
✓ E.	-	0-1	0-1	none	none	(68%)

Incorrect
Correct answer
E

68%
Answered correctly

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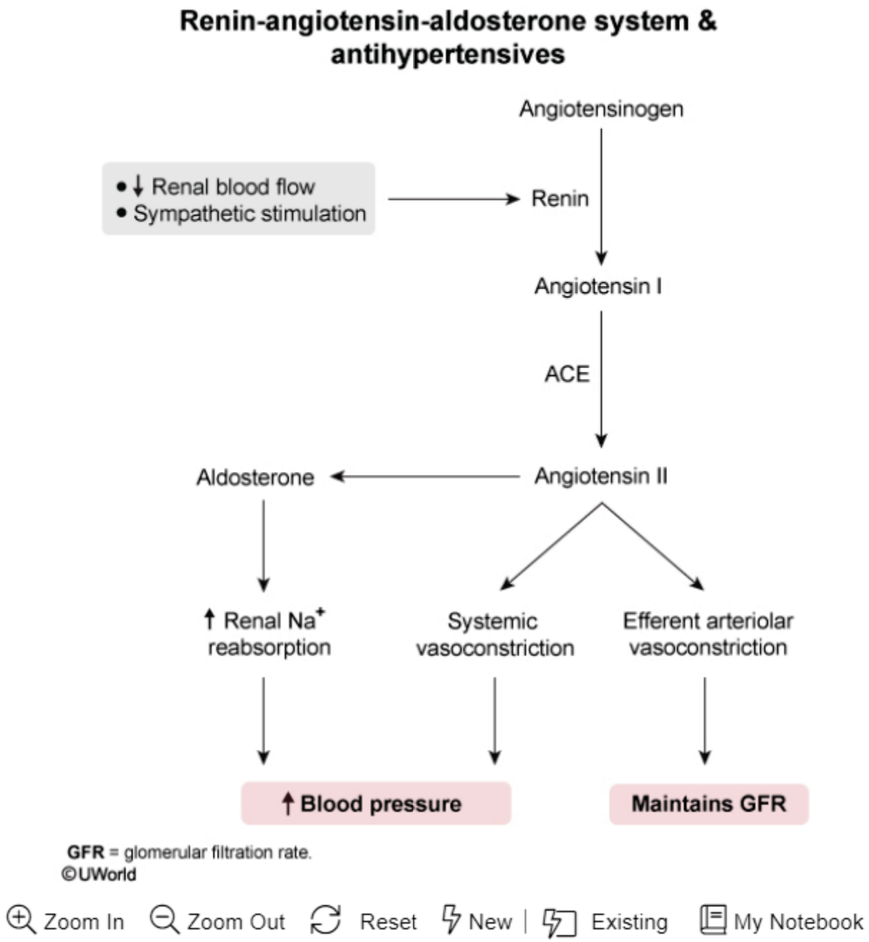
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Explanation

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E.	-	0-1	0-1	none	none	(68%)

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GFR = glomerular filtration rate.
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This patient has **widespread atherosclerosis** (cerebrovascular and coronary) and significant atherosclerotic risk factors (ie, hypertension, smoking). His persistent hypertension despite multiple medications suggests **renal artery stenosis** (RAS) due to atherosclerotic disease involving the renal arteries. Narrowing of the renal artery causes a reduction in renal blood flow and a decreased glomerular filtration rate (GFR) due to reduced hydrostatic pressure. This stimulates renin production, which leads to **angiotensin II** formation. Angiotensin II causes systemic vasoconstriction with a resultant rise in blood pressure, thereby increasing renal perfusion.

In the kidney, angiotensin II preferentially **constricts the efferent arteriole**, which increases glomerular filtration. Blockade of this response by **ACE inhibitors** (eg, ramipril) or angiotensin II receptor blockers (eg, losartan) causes the filtration pressure to fall, leading to a **reduced GFR**. In unilateral RAS, the normal kidney compensates for the decreased GFR, and overall creatinine clearance is maintained. However, patients with bilateral RAS often develop a rise in serum creatinine with initiation of ACE inhibitors. Because the glomeruli and renal tubules are otherwise normal, **urinalysis** is typically **unremarkable** (ie, no hematuria, proteinuria, or casts).

(Choice A) Acute renal failure and hypertension with red blood cell casts, hematuria, sterile pyuria, and proteinuria suggest glomerulonephritis. However, glomerulonephritis is often associated with systemic conditions (eg, lupus, recent infections), not ACE inhibitor use.

(Choice B) White blood cell casts, sterile pyuria, and urine eosinophils suggest acute interstitial nephritis, which often occurs after new medication introduction. However, it is often accompanied by rash, fever, and eosinophilia.

(Choice C) Crystal precipitation in the urine can cause kidney injury and hematuria but typically presents with flank pain. In addition, acyclovir (not ramipril) causes needle-shaped crystal precipitation in the urine.

(Choice D) Oval fat bodies and significant proteinuria are seen in nephrotic syndromes (eg, membranous nephropathy, minimal change disease), which can cause acute kidney injury and hyperlipidemia. However, patients typically have significant edema, and nephrotic syndromes are not associated with ACE inhibitor use.

Educational objective:

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systemic vasoconstriction with a resultant rise in blood pressure, thereby increasing renal perfusion.

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Educational objective:
In renal artery stenosis, increased production of angiotensin II causes increased systemic blood pressure (to increase renal perfusion) and preferential constriction of the glomerular efferent arteriole (to increase glomerular filtration). Patients with bilateral renal artery stenosis are dependent on this response to maintain renal function; initiation of ACE inhibitors or angiotensin II receptor blockers can precipitate acute renal failure. However, urinalysis is typically unremarkable (ie, no hematuria, proteinuria, or casts).

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A 54-year-old man is hospitalized after a planned abdominal surgery. One of his physicians administers a new drug whose mechanism of action you do not know. Shortly after administration of the drug the patient develops flushing, diaphoresis and nausea. His blood pressure is 100/70 mmHg and heart rate is 55/min. His pupils are constricted but reactive to light. This medication is most likely given for which of the following conditions?

- A. Urinary tract infection
- B. Urinary obstruction
- C. Atonic bladder
- D. Fluid overload
- E. Hypovolemic shock

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A 54-year-old man is hospitalized after a planned abdominal surgery. One of his physicians administers a new drug whose mechanism of action you do not know. Shortly after administration of the drug the patient develops flushing, diaphoresis and nausea. His blood pressure is 100/70 mmHg and heart rate is 55/min. His pupils are constricted but reactive to light. This medication is most likely given for which of the following conditions?

- A. Urinary tract infection (3%)
- ✗ B. Urinary obstruction (17%)
- ✓ C. Atonic bladder (69%)
- D. Fluid overload (5%)
- E. Hypovolemic shock (5%)

Incorrect
Correct answer
C

69%
Answered correctly

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Explanation

The patient described in this vignette displays symptoms associated with cholinergic agonists. These medications increase GI tract smooth muscle tone to produce nausea, vomiting, abdominal cramps and diarrhea. Cholinergic agonists decrease heart rate, cardiac conduction and contractility, and may result in bradycardia, partial or complete heart block, and hypotension. Cholinergic-associated peripheral vasodilatation decreases blood pressure due to the stimulation of endothelial nitric oxide synthesis. Cholinergic agonists also increase secretion, leading to excessive sweating, salivation and lacrimation. These drugs can cause dyspnea via bronchoconstriction (increased smooth muscle tone in the tracheobronchial tree) and increased bronchial secretion.

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There are several cholinergic agonists used in medicine. Bethanechol is a cholinergic agonist used to stimulate peristalsis in postoperative ileus. This drug is also used to treat non-obstructive urinary retention (atonic bladder). Carbachol and pilocarpine are used to lower intraocular pressure in glaucoma. Cholinergic-associated miosis causes the iris to move further from the cornea. This widens the anterior chamber angle and allows for better outflow of the aqueous humor.

(Choices A and B) Cholinergic agonists are not used to treat urinary tract infections or urinary obstruction.

(Choice D) Clinically evident volume overload is treated with loop diuretics. Cholinergic agents will not help this condition.

(Choice E) Hypovolemic shock is treated with IV fluids. Administering a cholinergic agent would likely worsen hypovolemic shock.

Educational Objective:
Cholinomimetics are indicated in non-obstructive urinary retention, paralytic ileus, and glaucoma. Their side effects include nausea, vomiting, abdominal cramps, diarrhea, dyspnea and increased secretions (sweating, lacrimation and salivation).

Pharmacology	Renal, Urinary Systems & Electrolytes	Urinary retention
Subject	System	Topic

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A 35-year-old pregnant woman at 8 weeks gestation comes to the emergency department due to persistent nausea and vomiting. The patient has had intermittent nausea for the past week and vomiting for the past 3 days. Now, she is unable to tolerate solids or liquids. Temperature is 36.7 C (98 F), blood pressure is 90/64 mm Hg, pulse is 108/min, and respirations are 14/min. Mucous membranes are dry and capillary refill time is delayed. Cardiac examination shows sinus tachycardia and no murmurs. The abdomen is nontender and nondistended. Compared to her baseline, which of the following sets of serum electrolyte concentration abnormalities are most likely present in this patient?

	Sodium	Potassium	Chloride	Bicarbonate
○ A.	↓	↓	↓	↑
○ B.	↓	Normal	↓	Normal
○ C.	Normal	↑	Normal	↓
○ D.	↑	Normal	↑	Normal
○ E.	Normal	↑	Normal	↑
○ F.	↓	↓	↓	↓

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	Sodium	Potassium	Chloride	Bicarbonate	
✓ A.	↓	↓	↓	↑	(71%)
✗ B.	↓	Normal	↓	Normal	(4%)
C.	Normal	↑	Normal	↓	(2%)
D.	↑	Normal	↑	Normal	(3%)
E.	Normal	↑	Normal	↑	(3%)
F.	↓	↓	↓	↓	(14%)

Incorrect
Correct answer
A

71%
Answered correctly

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Explanation

Hypokalemic, hypochloremic metabolic alkalosis

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A 35-year-old pregnant woman at 8 weeks gestation comes to the emergency department due to persistent nausea and vomiting. The patient has had intermittent nausea for the past week and vomiting for the past 3 days. Now, she is unable to tolerate solids or liquids. Temperature is 36.7 C (98 F), blood pressure is 90/64 mm Hg, pulse is 108/min, and respirations are 14/min. Mucous membranes are dry and capillary refill time is delayed. Cardiac examination shows sinus tachycardia and no murmurs. The abdomen is nontender and nondistended. Compared to her baseline, which of the following sets of serum electrolyte concentration abnormalities are most likely present in this patient?

	Sodium	Potassium	Chloride	Bicarbonate	
✓ A.	↓	↓	↓	↑	(71%)
✗ B.	↓	Normal	↓	Normal	(4%)
C.	Normal	↑	Normal	↓	(2%)
D.	↑	Normal	↑	Normal	(3%)
E.	Normal	↑	Normal	↑	(3%)
F.	↓	↓	↓	↓	(14%)

Incorrect
Correct answer
A

71%
Answered correctly

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Explanation

Hypokalemic, hypochloremic metabolic alkalosis

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Hypokalemic, hypochloremic metabolic alkalosis	
Common etiologies	• Gastric suction or severe vomiting • Loop or thiazide diuretic overuse
Pathophysiology	• Gastric or renal H^+ losses **initiate** alkalosis • Volume depletion activates RAAS • ↑ Renal K^+ & H^+ losses cause hypokalemia & **worsen** alkalosis • Relatively greater loss of Cl^- than Na^+ → profound Cl^- depletion • ↓ Cl^- impairs renal HCO_3^- excretion to **perpetuate** alkalosis
Management	• Remove or treat initiating factor • Cl^- replenishment with normal saline corrects alkalosis
RAAS = renin-angiotensin-aldosterone system.	

This patient has had **severe vomiting** (suggestive of hyperemesis gravidarum) and now has multiple signs of **volume depletion** (eg, dry mucous membranes, delayed capillary refill time, tachycardia). Vomiting causes a significant loss of gastric H^+ from the body, which leads to **increased serum HCO_3^-** (metabolic alkalosis). There is also loss of water and salt (relatively more Cl^- is lost than Na^+ due to high gastric quantity of HCl), leading to volume depletion that perpetuates the metabolic alkalosis and causes other electrolyte abnormalities.

Intravascular volume depletion decreases renal perfusion, resulting in activation of the **renin-angiotensin-aldosterone system**. Aldosterone stimulates Na^+ reabsorption and a lesser degree of passive Cl^- reabsorption in the distal tubules of the kidneys in an effort to increase blood volume. The relatively greater loss of Cl^- compared

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Intravascular volume depletion decreases renal perfusion, resulting in activation of the **renin-angiotensin-aldosterone system**. Aldosterone stimulates Na^+ reabsorption and a lesser degree of passive Cl^- reabsorption in the distal tubules of the kidneys in an effort to increase blood volume. The relatively greater loss of Cl^- compared to Na^+ from both the stomach and kidneys leads to a large Cl^- deficit and characteristic **hypochloremia**.

The aldosterone-mediated increase in Na^+ reabsorption comes at the expense of increased K^+ and H^+ excretion via the principal and alpha intercalated cells in the collecting duct. This leads to **hypokalemia** and exacerbation of the metabolic alkalosis. **Chloride depletion** then **perpetuates the metabolic alkalosis** because low tubular Cl^- concentration impairs HCO_3^- excretion via the pendrin pump on beta intercalated cells.

If the hypovolemia persists, it also provides nonosmotic stimulus for the secretion of antidiuretic hormone (ADH). The ADH secretion is considered appropriate because the body's priority is to restore itself to euvolemia; however, it leads to free water retention with **hyponatremia** and more profound hypochloremia.

Educational objective:
Severe vomiting characteristically causes hypokalemic, hypochloremic metabolic alkalosis. The metabolic alkalosis is initiated by loss of gastric H^+ from the body, worsened by hypovolemia-induced activation of the renin-angiotensin-aldosterone system, and perpetuated by profound gastric and renal losses of Cl^- that lead to hypochloremia and impaired renal HCO_3^- excretion. Hypokalemia primarily results from aldosterone-mediated renal K^+ losses.

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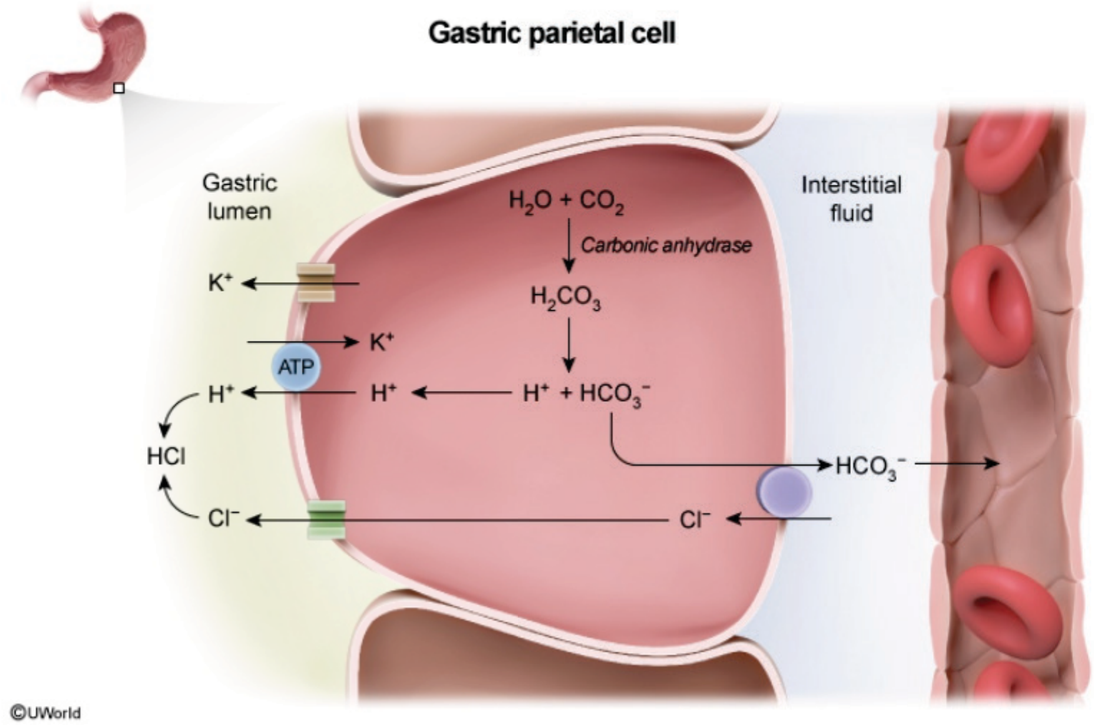
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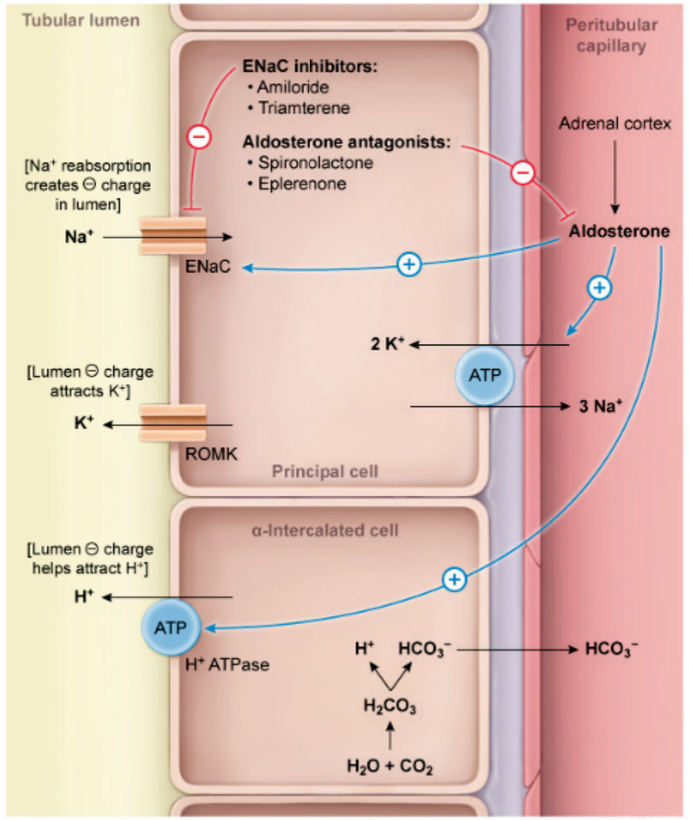
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Action of aldosterone in the collecting duct of the nephron



ENaC = epithelial sodium channel; **ROMK** = renal outer medullary potassium channel. ©UWorld

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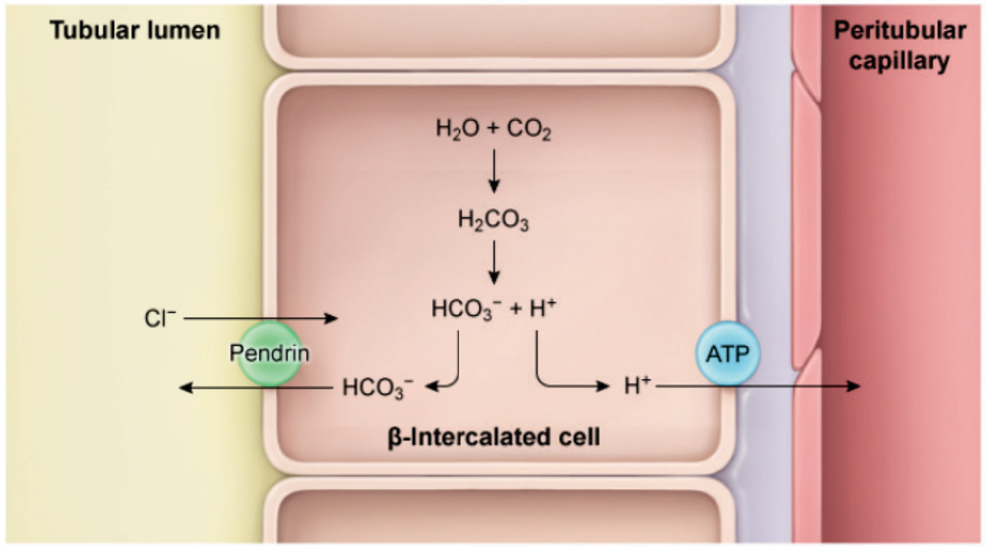
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Pendrin chloride/bicarbonate exchanger

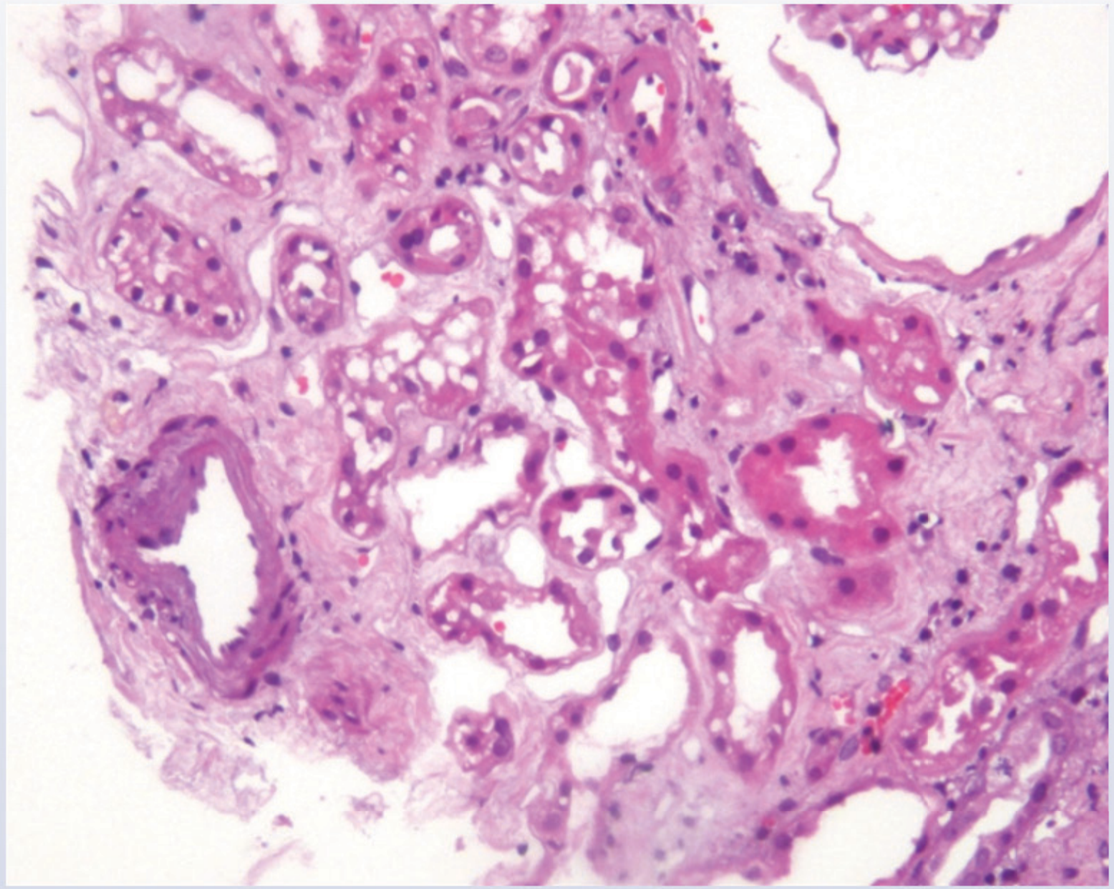


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A 32-year-old man is hospitalized with multiple fractures and internal bleeding following a motor vehicle collision. He is successfully resuscitated and taken to the operating room for fixation of a left femoral fracture. The patient's condition remains stable postoperatively, and he is transferred to the surgical floor. Blood pressure is 118/68 mm Hg and pulse is 88/min. He develops oliguria on the second day of hospitalization. Renal biopsy findings are shown in the image below.

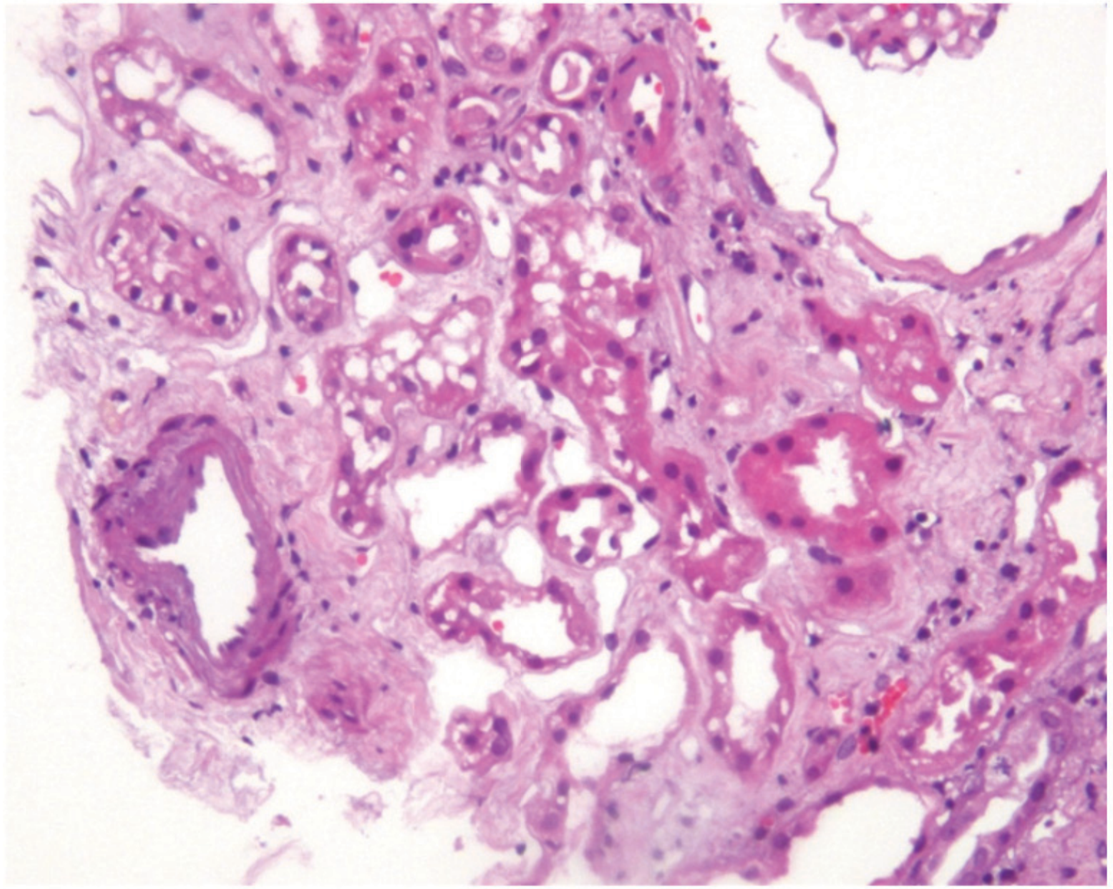


If the kidney biopsy were repeated 1 month from now, which of the following would most likely be seen?

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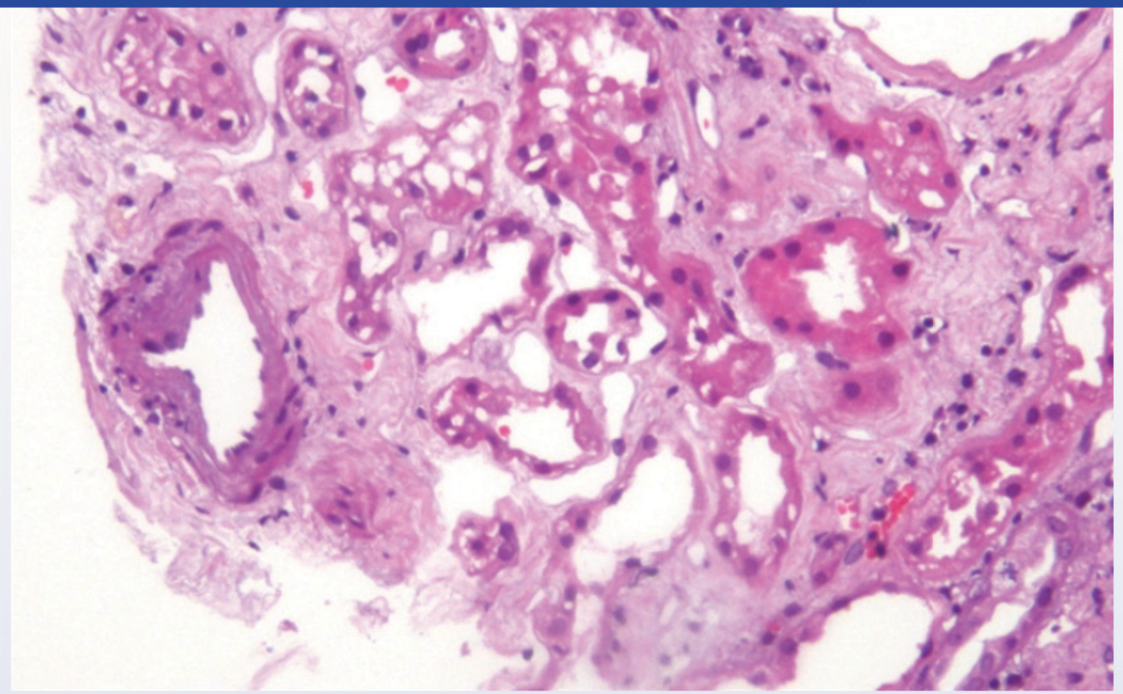
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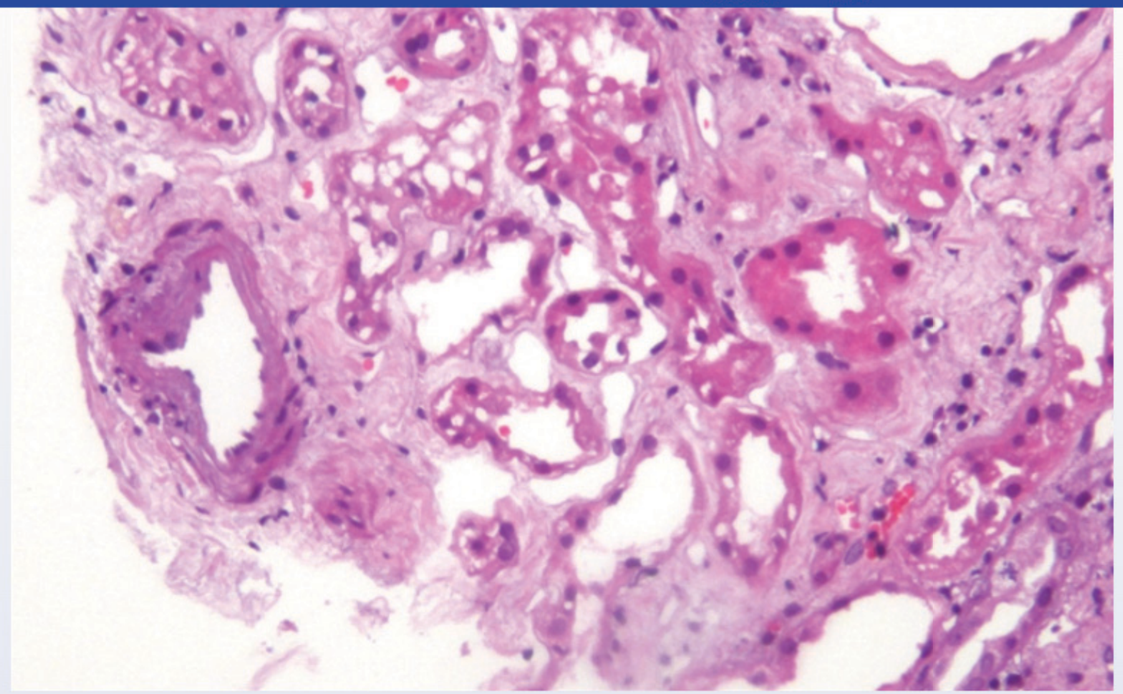


If the kidney biopsy were repeated 1 month from now, which of the following would most likely be seen?

- A. Diffuse mesangial sclerosis
- B. Glomerular epithelial proliferation
- C. Scarring and atrophy of the medulla
- D. Segmental glomerulosclerosis
- E. Tubular re-epithelization

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If the kidney biopsy were repeated 1 month from now, which of the following would most likely be seen?

- A. Diffuse mesangial sclerosis (6%)
- ✗ B. Glomerular epithelial proliferation (3%)
- C. Scarring and atrophy of the medulla (7%)
- D. Segmental glomerulosclerosis (4%)
- ✓ E. Tubular re-epithelization (76%)

Incorrect
Correct answer
E

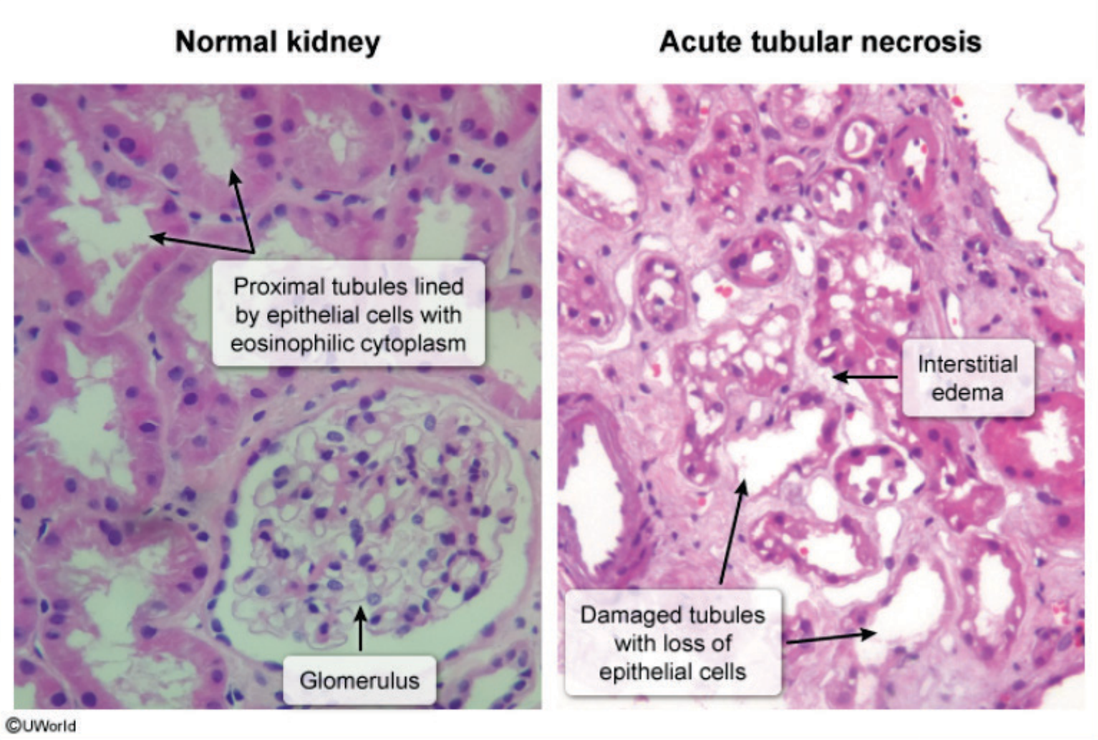
76%
Answered correctly

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Explanation



This patient has ischemic **acute tubular necrosis** (ATN) as a result of hypotension from hemorrhage. The clinical course of ATN may be divided into the initiation, maintenance (oliguric), and recovery phases.

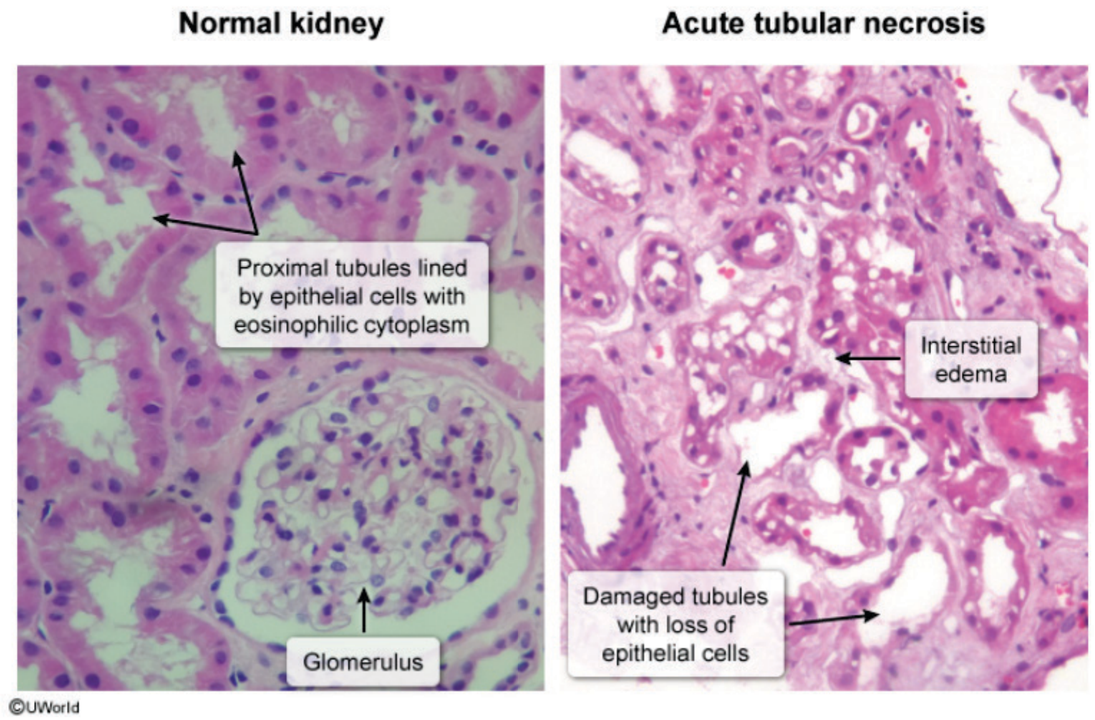
1. The **initiation phase** corresponds with the original ischemic or toxic insult and lasts approximately 24-36 hours. During this phase, only a slight decrease in urine output is present as renal tubular cell damage begins.

2. During the **maintenance phase**, tubular damage is fully established, resulting in oliguria, fluid overload, and electrolyte abnormalities (eg, hyperkalemia, metabolic acidosis). This phase usually lasts **1-2 weeks**, during

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Explanation

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1. The **initiation phase** corresponds with the original ischemic or toxic insult and lasts approximately 24-36 hours. During this phase, only a slight decrease in urine output is present as renal tubular cell damage begins.

2. During the **maintenance phase**, tubular damage is fully established, resulting in oliguria, fluid overload, and electrolyte abnormalities (eg, hyperkalemia, metabolic acidosis). This phase usually lasts **1-2 weeks**, during which the glomerular filtration rate remains well below normal with a corresponding rise in serum creatinine. Light microscopy shows **tubular epithelial necrosis**, sloughing of cells with **denuded basement membranes**, and casts containing degenerating cells and debris.

3. The **recovery phase** is characterized by the **re-epithelization** of tubules. The glomerular filtration rate recovers relatively quickly as the tubules clear of casts and debris. However, the tubular cells recover more gradually, resulting in transient polyuria and loss of electrolytes due to impaired tubular resorption and decreased renal concentrating ability. The majority of patients eventually have complete restoration of renal function.

(Choices A, B, and D) Diffuse mesangial sclerosis results in infantile nephrotic syndrome, whereas focal segmental glomerulosclerosis causes nephrotic syndrome in adolescents and adults and can be related to drug use (eg, heroin). Glomerular epithelial proliferation occurs in crescentic glomerulonephritis and diabetic nephropathy, among other diseases. These findings are not common in ATN.

(Choice C) Focal interstitial fibrosis causing medullary scarring and atrophy may be seen in a small number of patients, especially when ATN is accompanied by disruption of the tubular basement membrane. It is not, however, the most common outcome of ATN.

Educational objective:

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1. The **initiation phase** corresponds with the original ischemic or toxic insult and lasts approximately 24-36 hours. During this phase, only a slight decrease in urine output is present as renal tubular cell damage begins.

2. During the **maintenance phase**, tubular damage is fully established, resulting in oliguria, fluid overload, and electrolyte abnormalities (eg, hyperkalemia, metabolic acidosis). This phase usually lasts **1-2 weeks**, during which the glomerular filtration rate remains well below normal with a corresponding rise in serum creatinine. Light microscopy shows **tubular epithelial necrosis**, sloughing of cells with **denuded basement membranes**, and casts containing degenerating cells and debris.

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Educational objective:
Acute tubular necrosis is characterized by focal tubular epithelial necrosis with denuding of the basement membrane. Most patients experience tubular re-epithelization and regain normal renal function.

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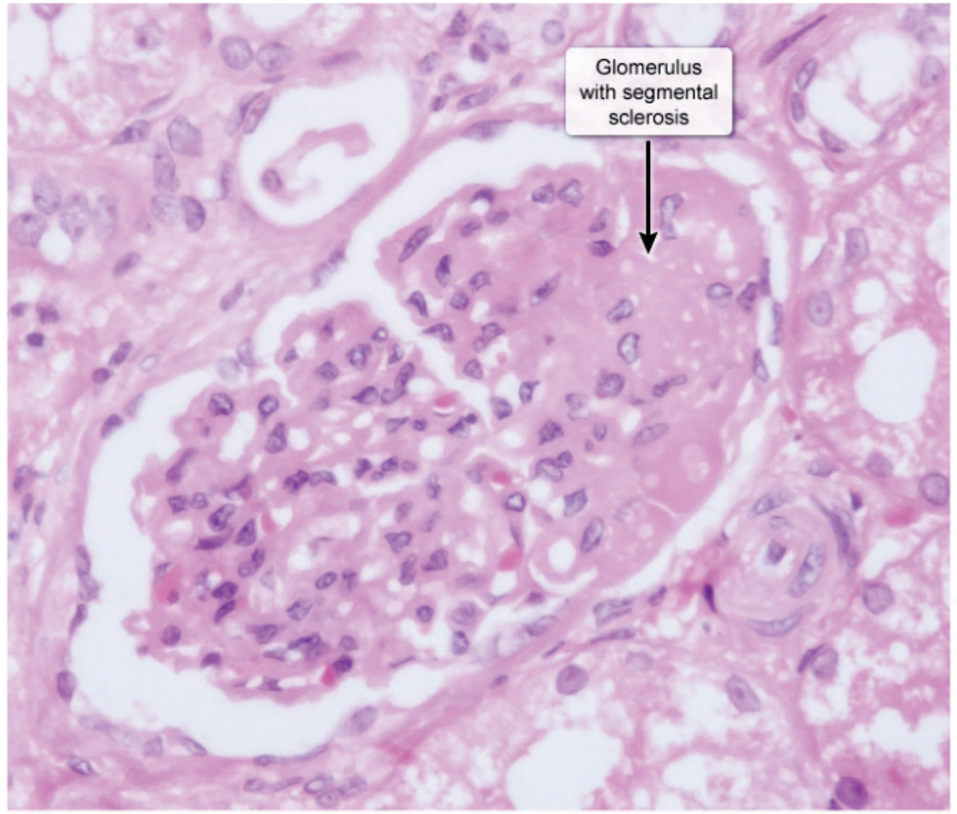
1. The **initiation phase** corresponds with the original ischemic or toxic insult and lasts approximately 24-36

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Focal segmental glomerulosclerosis



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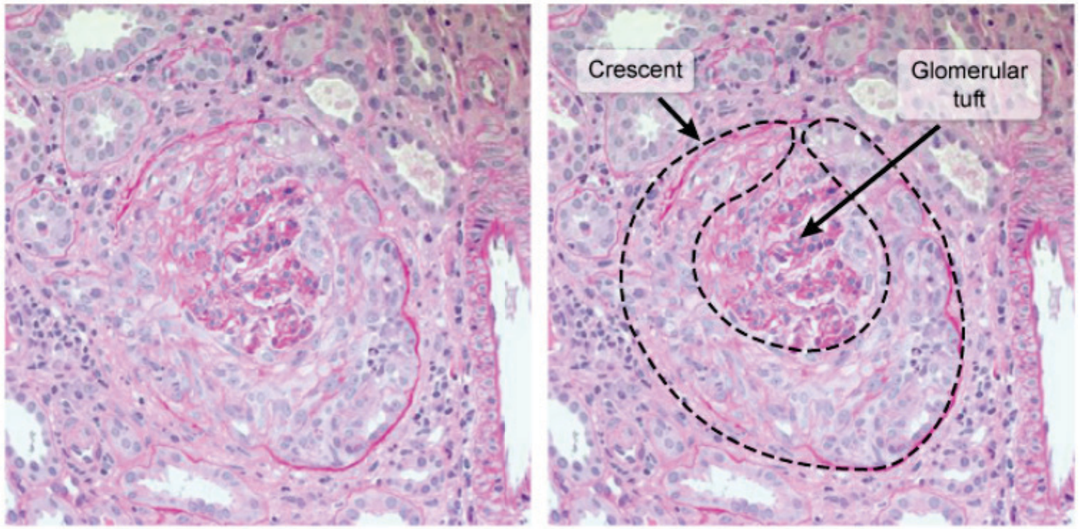
1. The **initiation phase** corresponds with the original ischemic or toxic insult and lasts approximately 24-36

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Crescentic glomerulonephritis



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membrane. Most patients experience tubular re-epithelization and regain normal renal function.

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A 64-year-old woman is evaluated for right hand pain after a fall from standing height. The patient has a 20-year history of type 2 diabetes mellitus complicated by diabetic nephropathy and advanced chronic kidney disease. X-ray of the right hand reveals no fractures, but it demonstrates subperiosteal resorption and new bone formation, particularly at the radial aspect of the middle phalanges. Laboratory studies show elevated serum parathyroid hormone, alkaline phosphatase, and phosphorus levels. If a bone biopsy is performed, which of the following findings would most likely be present in this patient?

	Osteoclasts	Osteoblasts
◯ A.	Decreased	Decreased
◯ B.	Decreased	Increased
◯ C.	Increased	Increased
◯ D.	Normal	Normal

Submit

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	Osteoclasts	Osteoblasts	
A.	Decreased	Decreased	(2%)
✗ B.	Decreased	Increased	(11%)
✓ C.	Increased	Increased	(82%)
D.	Normal	Normal	(4%)

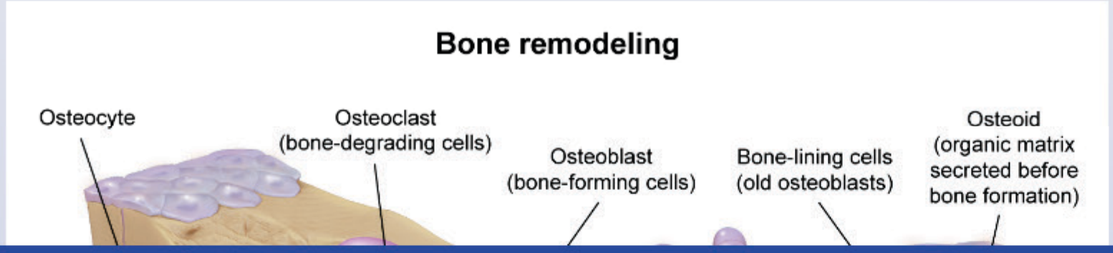
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Explanation

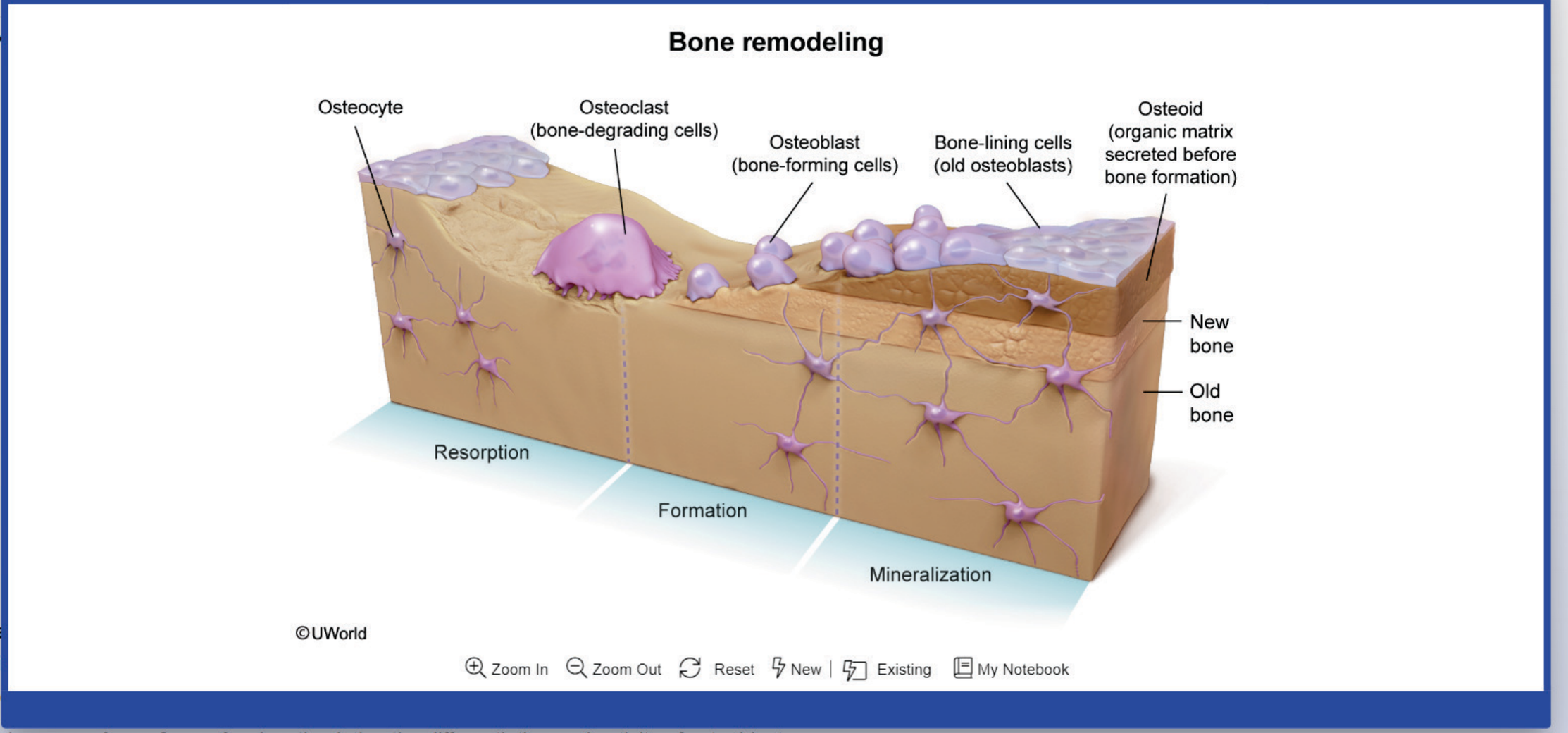


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- Increases **bone formation** by stimulating the differentiation and activity of osteoblasts

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Parathyroid hormone (PTH) plays an important role in bone remodeling by regulating the activity of osteoblasts (which secrete osteoid for bone formation) and osteoclasts (which resorb bone). PTH exerts the following **dual effects** on bone:

- Increases **bone formation** by stimulating the differentiation and activity of osteoblasts
- Increases **bone resorption** by transforming osteoblasts into osteoclasts

This balanced process allows for normal bone turnover but can become disrupted in conditions that alter PTH secretion, such as secondary hyperparathyroidism in patients with chronic kidney disease (CKD). In CKD, hypocalcemia, caused by decreased formation of active vitamin D and decreased renal phosphate excretion, triggers **PTH secretion** in an attempt to increase serum calcium. Despite releasing calcium from bones, this compensatory response is unable to fully normalize serum calcium (due to the failing kidneys) and therefore results in chronic PTH elevation (ie, loss of negative feedback).

Chronic PTH elevation leads to increased activity of both osteoclasts and osteoblasts; the increase in osteoclast activity exceeds that of osteoblasts, which results in **greater bone resorption than formation** (suggested by an elevated serum alkaline phosphatase). A potential consequence of this high bone turnover is **osteitis fibrosa cystica**, a form of renal osteodystrophy characterized by weakened bone caused by the replacement of mineralized bone with fibrous tissue.

Serum elevations in PTH, phosphorus, and alkaline phosphatase, in conjunction with the plain radiography finding of **subperiosteal resorption**, are typically sufficient for the diagnosis of osteitis fibrosa cystica. However, a bone biopsy would show an **increased** number of **osteoclasts and osteoblasts** throughout the bone trabeculae **(Choice D)**.

(Choice A) Excessive treatment of hyperparathyroidism can lead to chronically low PTH levels, which can cause adynamic bone disease. Adynamic bone disease is another form of renal osteodystrophy characterized by a low bone turnover state with decreased cellularity (ie, decreased numbers of both osteoblasts and osteoclasts).

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(Choice B) The combination of decreased osteoclasts and increased osteoblasts is rarely seen in bone disease.

Educational objective:
Osteitis fibrosa cystica is a form of renal osteodystrophy characterized by abnormally high bone turnover caused by chronic parathyroid hormone stimulation of osteoclasts to a greater degree than that of osteoblasts. Bone biopsy would show an increased number of both osteoclasts and osteoblasts.

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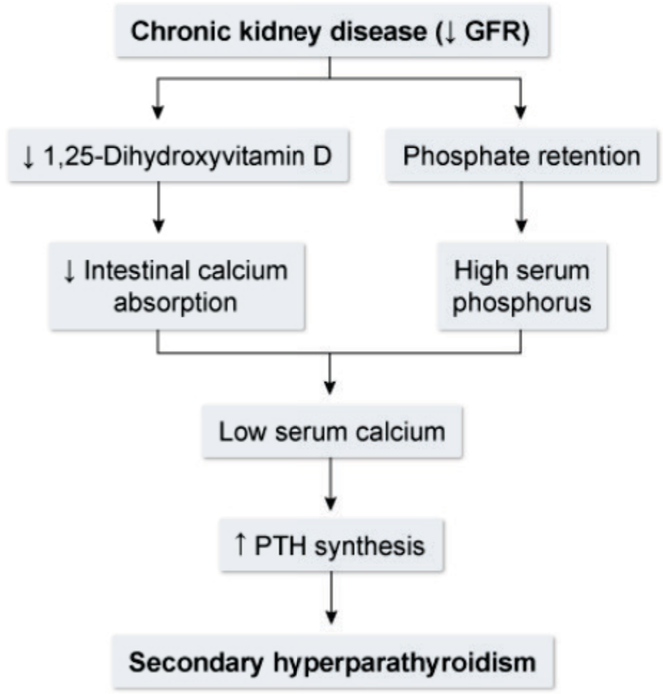
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GFR = glomerular filtration rate; **PTH** = parathyroid hormone.

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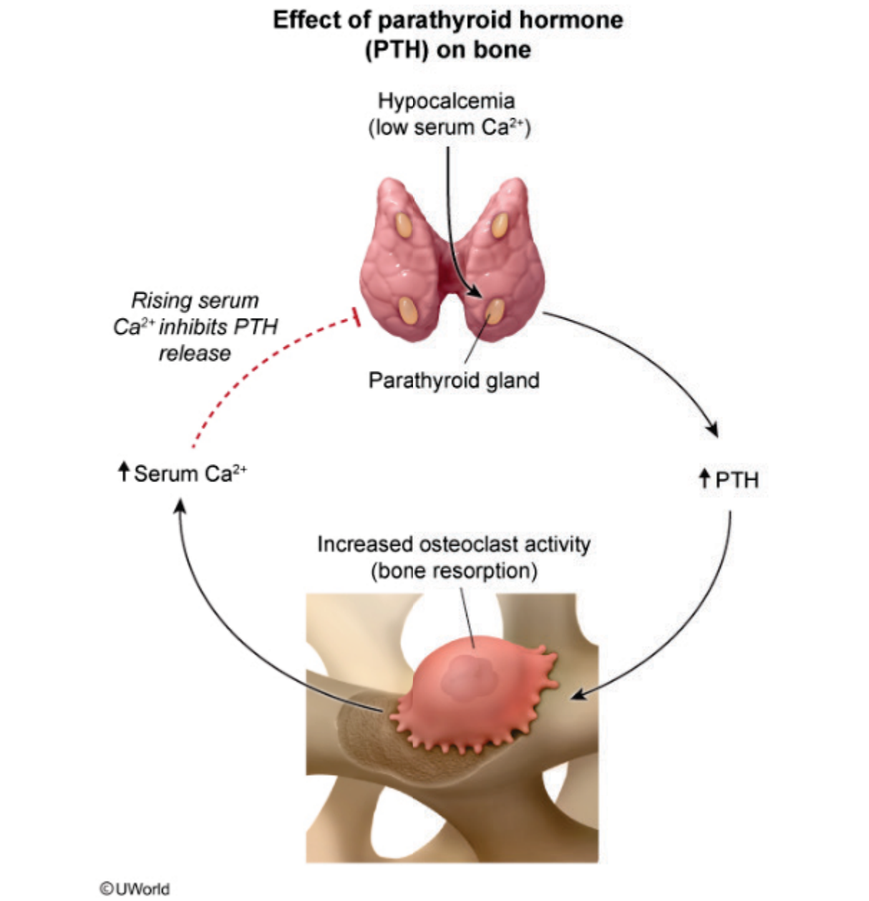
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A 57-year-old man comes to the hospital due to nausea, vomiting, and severe crampy pain in the right flank. He has had no fever or chills. Several days ago, the patient had similar, but less severe, pain that resolved spontaneously. Medical history is significant for type 2 diabetes mellitus, obesity, hyperlipidemia, hypertension, and gout. Temperature is 37 C (98.6 F), blood pressure is 160/100 mm Hg, and pulse is 98/min. Physical examination shows right flank tenderness. Blood urea nitrogen and serum creatinine are normal. Abdominal ultrasound reveals right-sided hydronephrosis and proximal ureteral dilation. Urinalysis in this patient would most likely reveal which of the following?

- A. Malignant cells
- B. Red blood cells
- C. Red blood cell casts
- D. Specific gravity of 1.002
- E. White blood cell casts

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- A. Malignant cells (3%)
- ✓ B. Red blood cells (61%)
- C. Red blood cell casts (12%)
- D. Specific gravity of 1.002 (13%)
- E. White blood cell casts (9%)

Correct

61%
Answered correctly

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Time Spent

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Explanation

This patient has acute, recurrent flank pain associated with ureteral dilation; this presentation is typical for acute **ureterolithiasis**. Although ultrasound is relatively sensitive for ureteral and calyceal dilation due to an obstructing stone **(hydronephrosis)**, small stones themselves may not be visible.

Kidney stones usually cause **disruption of the ureteral epithelium** with resulting gross or microscopic **hematuria**

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Explanation

This patient has acute, recurrent flank pain associated with ureteral dilation; this presentation is typical for acute **ureterolithiasis**. Although ultrasound is relatively sensitive for ureteral and calyceal dilation due to an obstructing stone **(hydronephrosis)**, small stones themselves may not be visible.

Kidney stones usually cause **disruption of the ureteral epithelium** with resulting gross or microscopic **hematuria** due to the presence of free red blood cells (RBCs) in the urine. When bleeding into the renal collecting system or lower urinary tract occurs, RBC **morphology is normal**. In contrast, glomerular bleeding (eg, glomerulonephritis) causes formation of RBC casts due to trapping of RBCs by precipitating Tamm-Horsfall protein **(Choice C)**; the cells are typically dysmorphic due to mechanical and osmotic trauma as they pass through the nephron.

Inspection of urine sediment in patients with acute ureterolithiasis may identify crystals corresponding to the type of stone. This patient has risk factors for uric acid stones, including gout and metabolic syndrome (obesity, diabetes mellitus, hyperlipidemia), and urinalysis may show polygonal uric acid crystals (which are morphologically distinct from the needle-shaped monosodium urate crystals seen in synovial fluid in acute gout).

(Choice A) Malignant cells can sometimes be identified on unstained microscopy of urine sediment in patients with urothelial carcinoma arising from the epithelium of the renal pelvis, ureters, or bladder. However, these malignancies typically present with painless hematuria rather than acute ureteral obstruction.

(Choice D) Urine specific gravity correlates with urine concentration, and a specific gravity of ≤1.003 indicates dilute urine; because kidney stones most commonly occur in concentrated urine (eg, >1.015), it is unlikely that a patient with an acute stone would have such a low specific gravity.

(Choice E) Occasional white blood cells may also be seen in ureterolithiasis, but overt pyuria suggests a urinary tract infection; white cell casts would be more characteristic of renal inflammation or infection (eg, acute interstitial nephritis, pyelonephritis).

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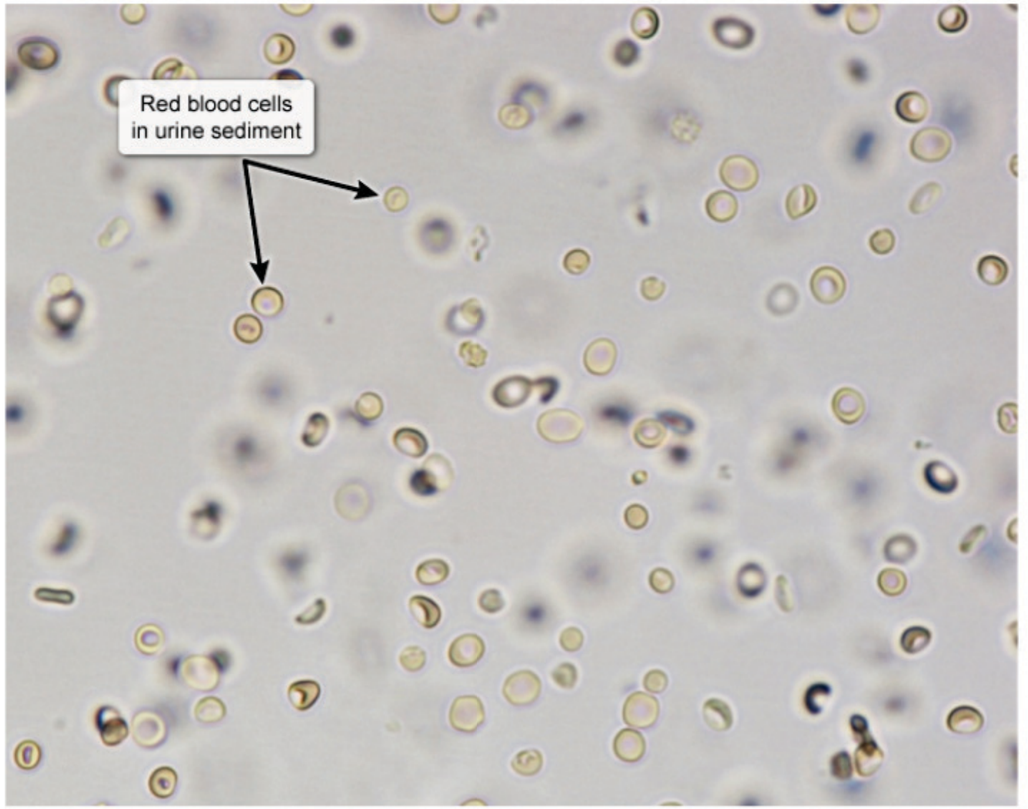
Educational objective:
Urine sediment in acute ureterolithiasis typically shows free red blood cells (hematuria) and crystals consistent with the type of stone. Ultrasound can reveal ureteral and calyceal dilation (hydronephrosis), but small stones themselves may not be visible.

Pathology Renal, Urinary Systems & Electrolytes Renal calculi

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Hematuria



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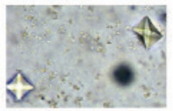
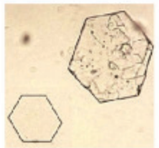
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Nephrolithiasis

Content	Frequency	Radiograph opacity	pH	Microscopic appearance
Calcium oxalate	70%-80%	↑↑	--	 • Octahedron (square with an "X" in the center)
Calcium phosphate			>7.0	• Elongated, wedge-shaped • Forms rosettes
Magnesium ammonium phosphate (struvite or triple phosphate)	15%	↑	>7.0	 • Rectangular prism ("coffin lids")
Uric acid	5%	--	<7.0	 • Yellow or red-brown, diamond or rhombus
Cystine	1%	↑	<7.0	 • Flat, yellow, **hexagonal**

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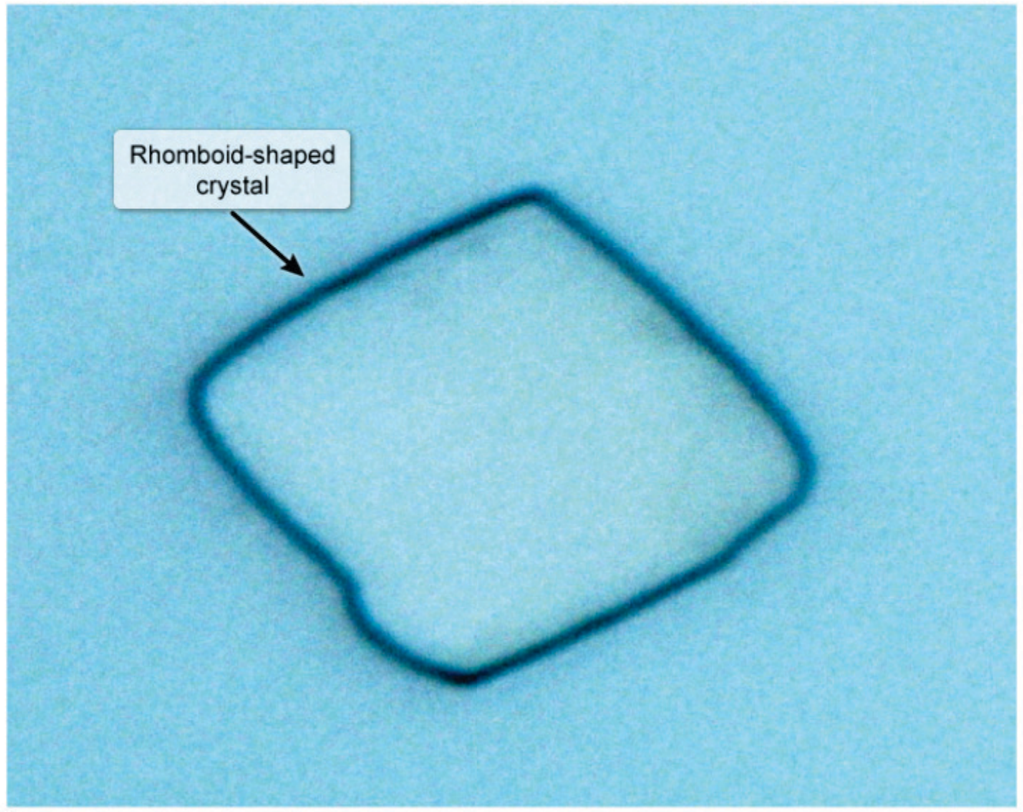
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Uric acid crystals



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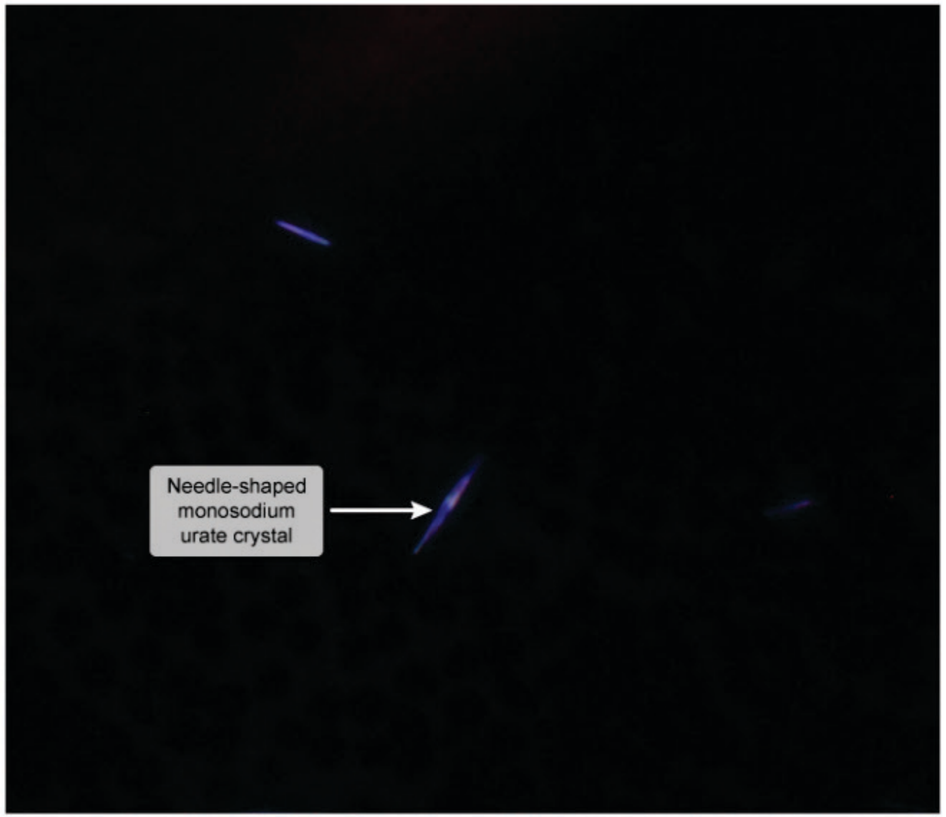
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Gout



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A 16-year-old girl is brought to the emergency department from home due to altered mental status. Her parents note that she was in her usual state of health at lunch, which was about 6 hours ago. Temperature is 38.3 C (100.9 F), blood pressure is 120/70 mm Hg, pulse is 104/min, and respirations are 30/min. Pulse oximetry is 97% on room air. The girl is disoriented and drowsy. Physical examination shows normal-sized reactive pupils and clear lungs. There is tenderness over the epigastric area. Laboratory studies are as follows:

Serum chemistry	
Sodium	140 mEq/L
Potassium	3.5 mEq/L
Chloride	104 mEq/L
Bicarbonate	14 mEq/L
Glucose	78 mg/dL
Lactic acid, venous blood	7.5 mmol/L

Which of the following is the most likely cause of this patient's findings?

- A. Ethanol intoxication
- B. Aspirin intoxication
- C. Carbon monoxide poisoning
- D. Diabetic ketoacidosis
- E. Pulmonary embolism

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Glucose	78 mg/dL
Lactic acid, venous blood	7.5 mmol/L

Which of the following is the most likely cause of this patient's findings?

- A. Ethanol intoxication (20%)
- ✓ B. Aspirin intoxication (54%)
- ✗ C. Carbon monoxide poisoning (5%)
- D. Diabetic ketoacidosis (18%)
- E. Pulmonary embolism (0%)

Incorrect
Correct answer
B

54%
Answered correctly

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Explanation

This patient with acutely altered mental status has an elevated anion gap and tachypnea, findings concerning for **salicylate intoxication**. Toxicity in children is usually due to accidental salicylate (eg, aspirin, wintergreen oil) ingestion but can be seen with intentional overdose in adolescents and adults.

Symptoms of acute salicylate overdose begin within a couple hours of ingestion and include:

- **Tinnitus** (eg, ringing/buzzing sound) is an early sign that can occur even with normal serum salicylate concentrations.
- **Hyperventilation** (causing a **primary respiratory alkalosis**) due to stimulation of the medullary respiratory center.
- **Nausea and vomiting** due to activation of the chemoreceptor trigger zone in the medulla and from direct gastric irritation (epigastric tenderness) as a result of decreased prostaglandin synthesis.
- Uncoupling of oxidative phosphorylation leads to **hyperthermia** and increased anaerobic metabolism. The resulting **increase in lactic acid** production causes a **primary metabolic acidosis** with an elevated anion gap (22 = 140 - [104 + 14]).
- **Altered mental status** can occur due to the direct effect of salicylates on the CNS and as a result of neuroglycopenia (cerebral glycolysis increases due to the oxidative phosphorylation impairment).

(Choice A) Ethanol intoxication causes slurred speech, nystagmus, decreased coordination, and CNS depression. It is associated with respiratory depression (not tachypnea).

(Choice C) Carbon monoxide poisoning causes flu-like symptoms, headaches, and altered mental status. An anion gap metabolic acidosis can occur due to increased lactate production. However, hyperthermia and tachypnea would not be expected. In addition, symptoms in only one household member would be unusual.

(Choice D) Insulin deficiency and hyperglycemia in type I diabetics can lead to diabetic ketoacidosis, which is

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gastric irritation (epigastric tenderness) as a result of decreased prostaglandin synthesis.

- Uncoupling of oxidative phosphorylation leads to **hyperthermia** and increased anaerobic metabolism. The resulting **increase in lactic acid** production causes a **primary metabolic acidosis** with an elevated anion gap (22 = 140 - [104 + 14]).
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(Choice D) Insulin deficiency and hyperglycemia in type I diabetics can lead to diabetic ketoacidosis, which is characterized by lipolysis, ketoacid production, and an anion gap metabolic acidosis. Abdominal pain and mental status changes can be seen. However, this patient's normal glucose level is inconsistent with this diagnosis.

(Choice E) Symptoms of pulmonary embolism include hypoxia, tachycardia, chest pain, and shortness of breath. However, this patient has no risk factors (eg, recent surgery, cancer), and an anion gap metabolic acidosis would not be seen.

Educational objective:
Acute salicylate toxicity causes a primary respiratory alkalosis and a primary metabolic acidosis with an anion gap due to increased lactate production. Symptoms include tinnitus, tachypnea, hyperthermia, vomiting, and altered mental status.

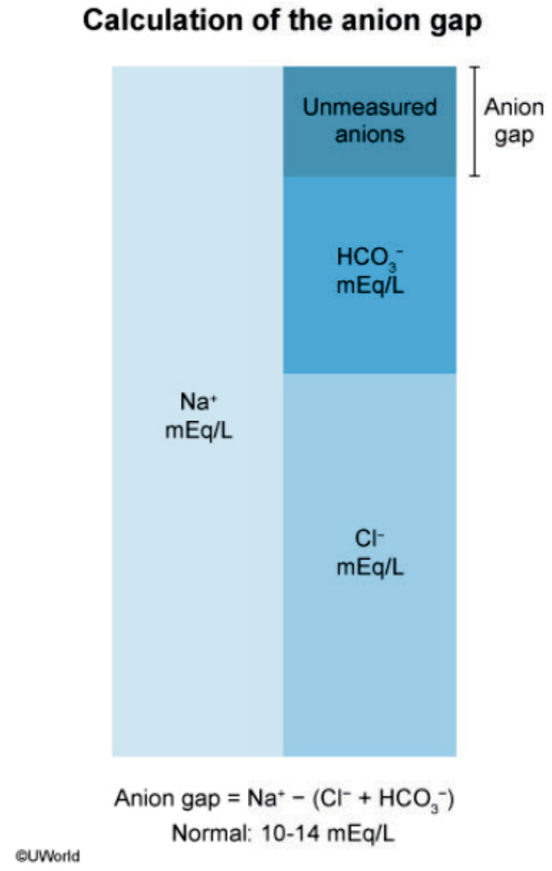
References

- Salicylates toxicity.

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- **Tinnitus** (eg, ringing/buzzing sound) is an early sign that can occur even with normal serum salicylate

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A 67-year-old man comes to the office due to generalized weakness, easy fatigability, anorexia, and intermittent nausea for the past several months. He also says that he is "itching and scratching a lot." Physical examination shows bilateral lower extremity pitting edema and skin excoriations. Laboratory results show a serum creatinine level of 3.4 mg/dL and a blood urea nitrogen level of 48 mg/dL. A renal biopsy is performed. Light microscopy of the tissue sample shows widespread narrowing of the renal arterioles with deposition of homogeneous, glassy material in the vessel walls that stains pink with periodic acid-Schiff (PAS) stain. This patient most likely has which of the following underlying conditions?

- A. Atheroembolic renal disease
- B. Diabetes mellitus
- C. Malignant hypertension
- D. Multiple myeloma
- E. Rapidly progressive glomerulonephritis

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- A. Atheroembolic renal disease (7%)
- ✓ B. Diabetes mellitus (43%)
- C. Malignant hypertension (23%)
- D. Multiple myeloma (16%)
- E. Rapidly progressive glomerulonephritis (8%)

Correct

43% Answered correctly

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Explanation

This patient's symptoms (eg, fatigue, weakness, itching) are most likely due to accumulation of uremia toxins secondary to progressive **chronic kidney disease**. His renal biopsy shows deposition of eosinophilic hyaline material in the intima and media of small arteries and arterioles, which is characteristic of **hyaline arteriolosclerosis**. It is typically seen in patients with untreated or poorly controlled **hypertension** (HTN) or **diabetes mellitus**. Chronic/repetitive endothelial injury caused by hemodynamic stress or hyperglycemia causes

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Explanation

This patient's symptoms (eg, fatigue, weakness, itching) are most likely due to accumulation of uremia toxins secondary to progressive **chronic kidney disease**. His renal biopsy shows deposition of eosinophilic hyaline material in the intima and media of small arteries and arterioles, which is characteristic of **hyaline arteriolosclerosis**. It is typically seen in patients with untreated or poorly controlled **hypertension** (HTN) or **diabetes mellitus**. Chronic/repetitive endothelial injury caused by hemodynamic stress or hyperglycemia causes leakage of plasma constituents across the vascular endothelium and stimulates smooth muscle cell (SMC) proliferation and excessive extracellular matrix production.

(Choice A) Atheroembolic renal disease typically occurs after manipulation of the aorta (eg, abdominal aortic aneurysm repair) in adults with widespread atherosclerosis. Atheroemboli with cholesterol clefts would be seen within the arterial lumen.

(Choice C) Malignant hypertension (extreme or rapidly developing hypertension) causes fibrinoid necrosis and hyperplastic arteriolosclerosis. Fibrinoid necrosis is characterized by localized destruction of the vascular wall with a circumferential ring of pink, amorphous material surrounding the lumen. Hyperplastic arteriolosclerosis consists of onion-like, concentric thickening of the walls of arterioles due to laminated layers of SMCs with intervening basement membrane reduplication (onion skinning). This patient's lack of concentric SMC thickening and absence of vascular necrosis are more suggestive of hyaline arteriolosclerosis.

(Choice D) Nephropathy in multiple myeloma is most often due to excess excretion of free light chains (Bence Jones proteins) that precipitate with Tamm-Horsfall protein to form obstructing tubular casts (cast nephropathy). These casts are seen as amorphous hyaline material in the tubular lumen.

(Choice E) Rapidly progressive glomerulonephritis (RPGN) is characterized by the formation of glomerular crescents composed of proliferating parietal cells, lymphocytes, macrophages, and fibrin. RPGN may occur in the absence of a systemic vasculitic syndrome; therefore, renal arteriolar lesions are not a defining feature

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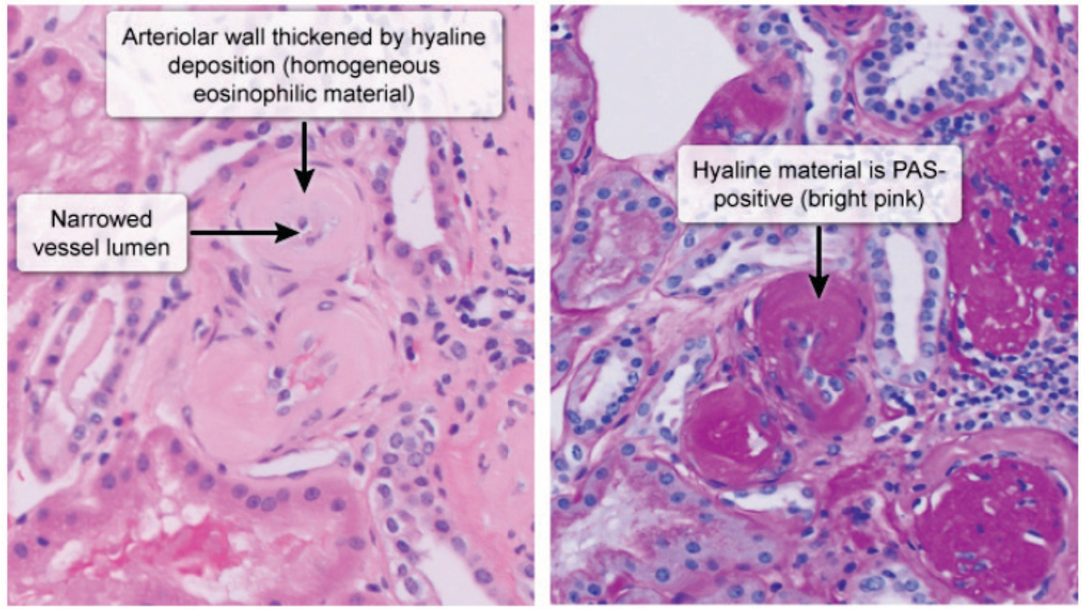
Educational objective:
Homogeneous deposition of eosinophilic hyaline material in the intima and media of small arteries and arterioles characterizes hyaline arteriolosclerosis. This is typically produced by untreated or poorly controlled hypertension and/or diabetes.

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D. Multiple myeloma (16%)

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Hyaline arteriolosclerosis



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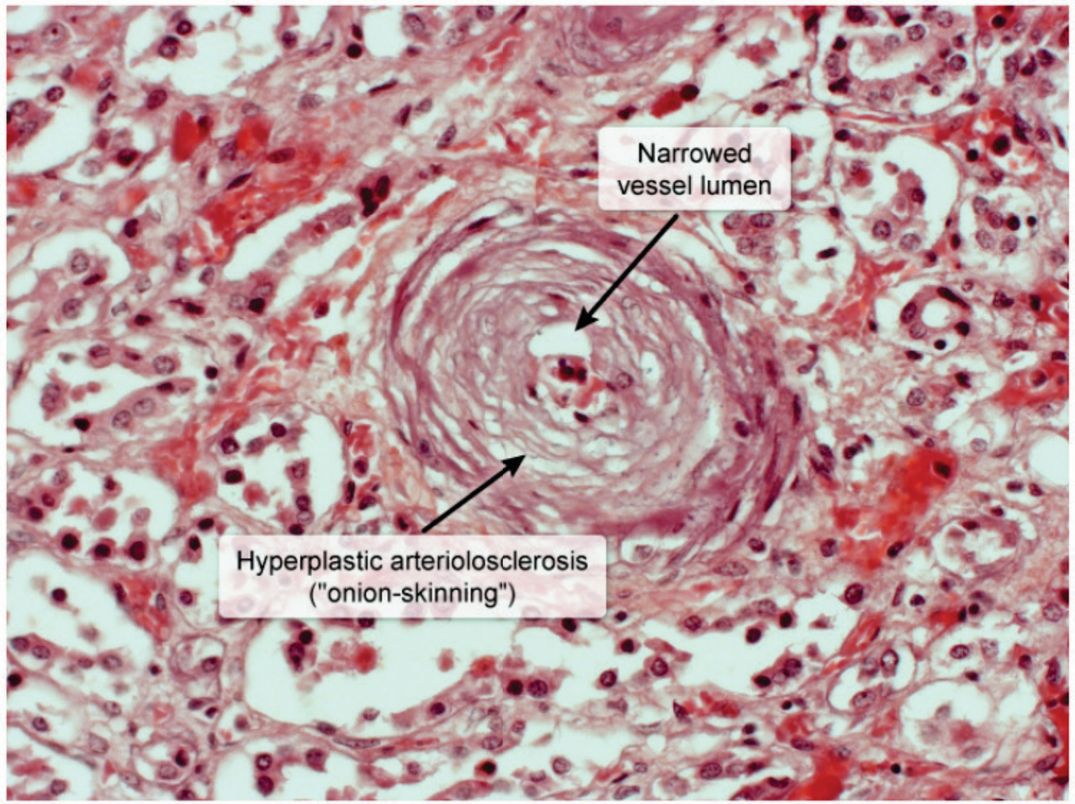
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Malignant hypertension



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A 64-year-old man who recently moved to the area comes to the office for a new patient evaluation. He has chronic low back pain, resulting from an injury 8 years ago, for which he uses several over-the-counter analgesics. Most recently, the patient has been taking naproxen daily. He has no other joint pain, fever, rash, urinary symptoms, or other medical conditions. Blood pressure is 135/70 mm Hg and pulse is 78/min. Examination shows trace lower extremity edema. Neurologic and musculoskeletal examinations reveal no abnormalities. Laboratory results show blood counts within normal limits, blood urea nitrogen of 12 mg/dL, and serum creatinine of 2.0 mg/dL. Urinalysis reveals 1+ protein and 3-4 white blood cells/hpf. Renal ultrasound demonstrates bilateral shrunken and irregular kidneys with a few papillary calcifications. Which of the following is the most likely cause of this patient's renal dysfunction?

- A. Chronic interstitial nephritis
- B. Chronic pyelonephritis
- C. Crystal nephropathy
- D. Focal segmental glomerular sclerosis
- E. Ischemic tubular necrosis
- F. Renal artery stenosis

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- ✓ A. Chronic interstitial nephritis (61%)
- ✗ B. Chronic pyelonephritis (7%)
- C. Crystal nephropathy (2%)
- D. Focal segmental glomerular sclerosis (3%)
- E. Ischemic tubular necrosis (16%)
- F. Renal artery stenosis (8%)

Incorrect
Correct answer
A

61%
Answered correctly

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Explanation

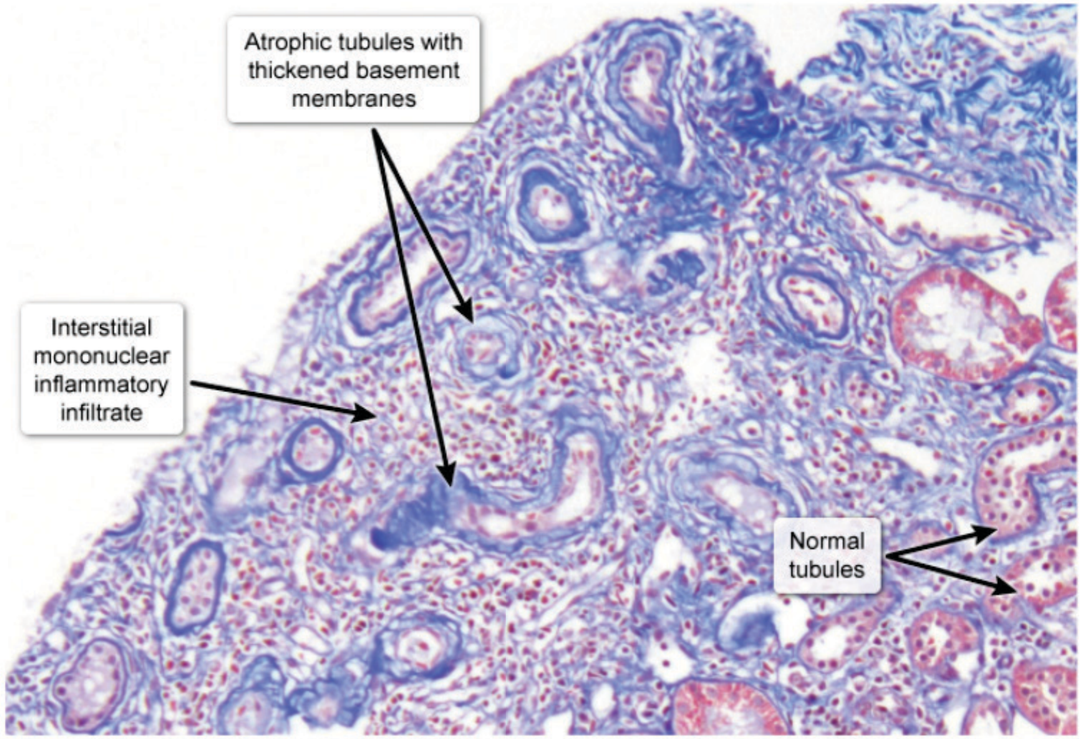
Chronic interstitial nephritis

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E. Ischemic tubular necrosis (16%)

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Chronic interstitial nephritis



Trichrome stain

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Over-the-counter analgesics such as nonsteroidal anti-inflammatory drugs (**NSAIDs**) can cause renal failure (**analgesic nephropathy**) if taken in large amounts over extended periods. Affected patients typically have a modest elevation in serum creatinine, mild proteinuria, and evidence of tubular dysfunction (polyuria, nocturia). Microscopic hematuria and sterile pyuria (white cells without bacteria) may also be seen on urinalysis.
NSAIDs concentrate in the renal medulla along the medullary osmotic gradient, with higher levels in the papillae. These drugs uncouple oxidative phosphorylation and increase oxidative stress, resulting in damage to tubular and vascular endothelial cells. Prolonged use results in **chronic interstitial nephritis** visualized as patchy interstitial inflammation with subsequent tubular atrophy and fibrosis, papillary necrosis, and scarring. Grossly, the kidneys appear shrunken with irregular contours and distortion of the caliceal architecture. NSAIDs also decrease prostaglandin synthesis, causing renal vasoconstriction which further increases the risk of **ischemic papillary necrosis**.

(Choice B) Chronic pyelonephritis can also cause chronic interstitial nephritis with papillary necrosis. However, urinalysis would be expected to demonstrate evidence of infection (eg, bacteria, nitrites, marked pyuria), and the patient would likely have flank pain and fever.

(Choice C) Acute crystal nephropathy presents with renal failure, and patients often have nausea, vomiting, or flank pain. Chronic crystalline nephropathy is most commonly seen in patients with gout or hyperuricemia secondary to urate deposition in the medullary interstitium.

(Choice D) Focal segmental glomerular sclerosis (FSGS) presents with nephrotic-range proteinuria. Drug-related secondary FSGS has been reported with the use of anabolic steroids or heroin but not NSAIDs.

(Choice E) Ischemic tubular necrosis usually occurs acutely after a prolonged period of hypotension (eg, sepsis, major surgery); muddy brown casts would be expected on urinalysis.

(Choice F) Symptoms of renal artery stenosis include resistant hypertension, recurrent flash pulmonary edema, and chronic kidney disease. The absence of hypertension and history of NSAID use are more consistent with chronic interstitial nephritis.

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(Choice F) Symptoms of renal artery stenosis include resistant hypertension, recurrent flash pulmonary edema, and chronic kidney disease. The absence of hypertension and history of NSAID use are more consistent with chronic interstitial nephritis.

Educational objective:
Analgesic nephropathy is a form of chronic kidney disease caused by prolonged, heavy intake of nonsteroidal anti-inflammatory drugs and/or acetaminophen. Pathologic characteristics include chronic interstitial nephritis and papillary necrosis.

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A 45-year-old man with a history of chronic alcohol use disorder is brought to the emergency room due to altered mental status. The patient appears malnourished. He is given thiamine, folic acid, a multivitamin, and dextrose-containing intravenous fluids. However, the patient develops marked muscle weakness a few hours later. Laboratory studies reveal a serum phosphate concentration of 0.5 mg/dL (normal: 2.5-4.5). Which of the following is the most likely cause of this patient's low serum phosphate level?

- A. Decreased renal proximal tubular reabsorption
- B. Increased colonic excretion of phosphate
- C. Increased extracellular binding with calcium
- D. Increased uptake by bone cells
- E. Redistribution of phosphate into hepatic and muscle cells

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- A. Decreased renal proximal tubular reabsorption (25%)
- ✗ B. Increased colonic excretion of phosphate (5%)
- C. Increased extracellular binding with calcium (20%)
- D. Increased uptake by bone cells (3%)
- ✓ E. Redistribution of phosphate into hepatic and muscle cells (45%)

Incorrect
Correct answer
E

45%
Answered correctly

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Explanation

Causes of hypophosphatemia	
Internal redistribution	• Increased insulin secretion (especially refeeding malnourished patients) • Acute respiratory alkalosis (stimulates glycolysis) • Hungry bone syndrome (after parathyroidectomy)
Decreased	• Chronic poor intake

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Internal redistribution	• Increased insulin secretion (especially refeeding malnourished patients) • Acute respiratory alkalosis (stimulates glycolysis) • Hungry bone syndrome (after parathyroidectomy)
Decreased intestinal absorption	• Chronic poor intake • Aluminum- or magnesium-containing antacids (bind phosphate) • Steatorrhea or chronic diarrhea
Increased urinary excretion	• Primary & secondary hyperparathyroidism • Vitamin D deficiency (↓ GI absorption, ↑ urinary excretion) • Primary renal phosphate wasting syndromes • Fanconi syndrome

Phosphorus is involved in multiple biologic processes, including cellular energy metabolism, bone formation, and acid-base homeostasis. Although biologically active phosphorus is largely found intracellularly, serum phosphorus levels are often reflective of available body stores and are maintained through the action of hormones (eg, parathyroid hormone, calcitriol, FGF-23) on the small intestines, bones, and kidneys.

Malnourishment (eg, due to chronic alcohol use disorder) results in the depletion of phosphate, although serum levels may remain normal due to transcellular shifts. Reintroduction of **carbohydrates** (ie, dextrose-containing intravenous fluids) increases insulin secretion, which stimulates the **redistribution of phosphate** from the serum **into muscle and hepatic cells** for use during glycolysis (eg, **formation of ATP**, 2-3 diphosphoglycerate). This leads to profound hypophosphatemia; lack of adequate intracellular phosphate can result in failure of cellular energy metabolism, producing the clinical features of refeeding syndrome (eg, **muscular weakness**, arrhythmias, congestive heart failure).

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(Choice A) Increased parathyroid hormone reduces the proximal tubular reabsorption of phosphorus. Although hyperparathyroidism results in hypophosphatemia, this occurs over a prolonged period and would not occur acutely after infusion of dextrose-containing fluids.

(Choice B) Although chronic diarrhea can cause hypophosphatemia, it predominantly occurs from reduced intestinal absorption of phosphorus, not increased excretion (only a small fraction of total body phosphorus is excreted into the intestines and lost in the feces). Furthermore, this patient is not having diarrhea.

(Choice C) Phosphorus can combine with calcium to form salts, which can be deposited in the skin or other organs (ie, dystrophic calcification). However, this typically occurs in the setting of hyperphosphatemia (not hypophosphatemia) in end-stage renal disease.

(Choice D) Hungry bone syndrome causes hypophosphatemia and hypocalcemia due to the rapid formation of bone after parathyroidectomy in a patient with chronic hyperparathyroidism. However, significant hypocalcemia typically results in tetany, not diffuse weakness, and this disorder usually occurs in the early postoperative period (2-4 days)

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Educational objective:
Refeeding syndrome occurs after the reintroduction of carbohydrates in patients with chronic malnourishment, which stimulates insulin secretion and drives phosphorus intracellularly in an effort to maintain cellular energy metabolism (eg, ATP production); this redistribution of phosphorus can result in severe hypophosphatemia.

Physiology Renal, Urinary Systems & Electrolytes Hypophosphatemia

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A 4-year-old girl developed acute-onset colicky abdominal pain, vomiting, and loose bloody stools during a family vacation. She was treated with supportive care and began to feel better. A few days later, her parents bring her to the emergency department because she has urinated only once in the past 10 hours and the urine was red. Physical examination shows conjunctival pallor but is otherwise normal. Laboratory studies are as follows:

Hemoglobin	7.8 g/dL
Platelets	80,000/mm^3
Creatinine	1.7 mg/dL

Urinalysis shows proteinuria and hematuria. Which of the following mechanisms is the most likely cause of this patient's condition?

- A. Microthrombi in small blood vessels
- B. Streptococcal antigen-associated glomerular damage
- C. Systemic IgA-mediated vasculitis
- D. Vasculitis involving medium arteries
- E. Widespread activation of the coagulation cascade

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Platelets	80,000/mm^3
Creatinine	1.7 mg/dL

Urinalysis shows proteinuria and hematuria. Which of the following mechanisms is the most likely cause of this patient's condition?

- ✓ A. Microthrombi in small blood vessels (43%)
- ✗ B. Streptococcal antigen-associated glomerular damage (11%)
- C. Systemic IgA-mediated vasculitis (31%)
- D. Vasculitis involving medium arteries (3%)
- E. Widespread activation of the coagulation cascade (10%)

Incorrect
Correct answer
A

43%
Answered correctly

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Explanation

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Hemolytic uremic syndrome	
Etiology	**Shiga toxin–producing bacteria** • *Escherichia coli* O157:H7 • *Shigella*
Clinical features	• Antecedent diarrheal illness (often bloody) • Hemolytic anemia with schistocytes • Thrombocytopenia • Acute kidney injury

This patient with a recent history of loose bloody stools now has anemia, thrombocytopenia, and signs of acute kidney injury. This presentation is consistent with diarrhea-associated **hemolytic uremic syndrome (HUS)**, a major cause of acute renal failure in young children.

Most cases are due to intestinal infection by **Shiga toxin** (verotoxin)-producing organisms (eg, *Escherichia coli* **O157:H7**, ***Shigella*** *dysenteriae*). These toxins injure the endothelium of preglomerular arterioles and glomerular capillaries, leading to platelet activation and aggregation and the formation of microthrombi.

Platelet consumption causes **thrombocytopenia** (platelets <140,000/mm^3), but there is typically no purpura or active bleeding. Erythrocytes passing through the damaged capillaries suffer shear injury and are broken down to schistocytes, causing **microangiopathic hemolytic anemia** (eg, conjunctival pallor). Extensive damage to the renal vasculature results in **acute kidney injury** (eg, oliguria/anuria, hematuria, increased creatinine).

(Choice B) Poststreptococcal glomerulonephritis develops approximately 1-3 weeks following a cutaneous or pharyngeal infection by a nephritogenic strain of group A β-hemolytic streptococci. It is caused by an immune response against streptococcal antigens that deposit in the glomerulus. Patients have oliguria, hematuria, proteinuria, edema, and hypertension. Anemia is not commonly seen.

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	• Acute kidney injury

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(Choice C) Systemic IgA-mediated vasculitis is characteristic of Henoch-Schönlein purpura (HSP), a leukocytoclastic vasculitis that typically involves small blood vessels of the skin, kidneys, intestines, and joints. Although HSP can cause abdominal pain and hematuria, platelet count is usually normal. In addition, the absence of palpable purpura and joint symptoms makes HSP unlikely in this patient.

(Choice D) Kawasaki disease (mucocutaneous lymph node syndrome) is a vasculitis of medium arteries that classically affects young children. The main symptoms are high fever, conjunctivitis, cervical lymphadenopathy, periungual desquamation, and mucocutaneous changes (eg, strawberry tongue).

(Choice E) Disseminated intravascular coagulation refers to massive, widespread activation of the coagulation cascade due to release of procoagulant substances caused by sepsis, malignancy, or trauma. These patients

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(Choice E) Disseminated intravascular coagulation refers to massive, widespread activation of the coagulation cascade due to release of procoagulant substances caused by sepsis, malignancy, or trauma. These patients usually have bleeding, petechiae, and bruising due to concomitant fibrinolysis and consumption of platelets and coagulation factors.

Educational objective:

Hemolytic uremic syndrome is a common cause of acute renal failure in children. It is characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. Most cases develop following a diarrheal illness caused by Shiga toxin-producing organisms (eg, *Escherichia coli* O157:H7, *Shigella dysenteriae)*.

References

- Shiga toxins and the pathophysiology of hemolytic uremic syndrome in humans and animals.

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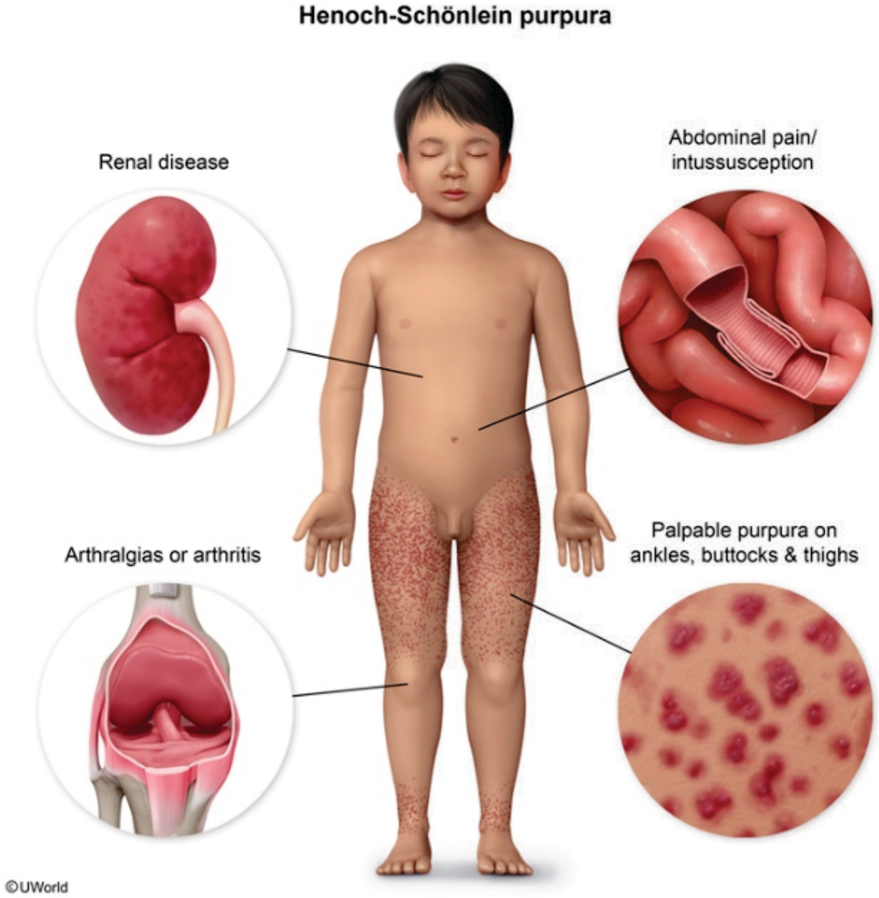
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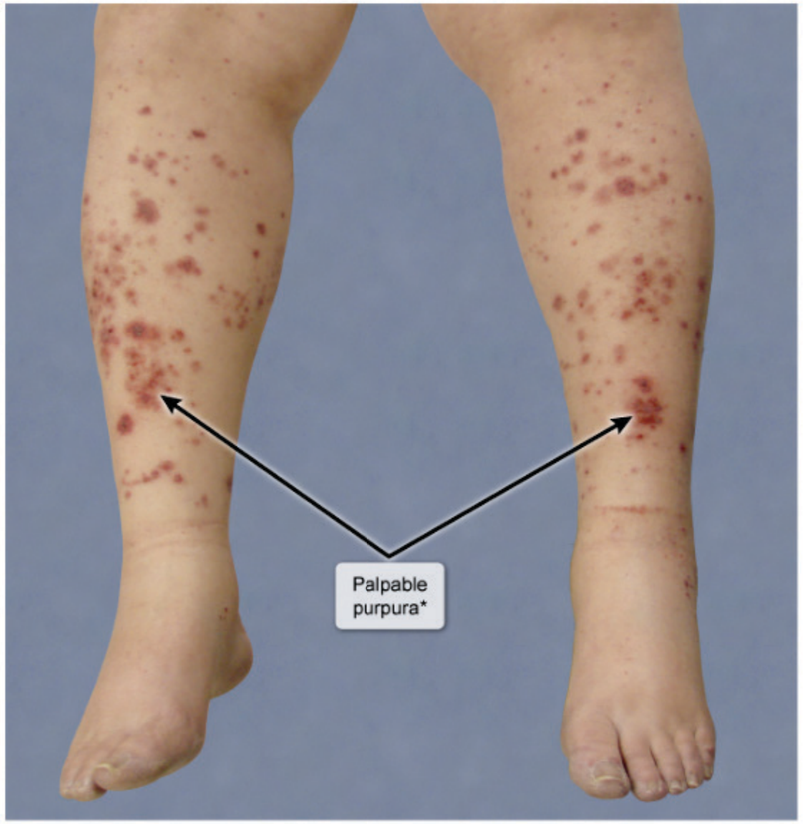
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microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. Most cases develop following a

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Henoch-Schönlein purpura



*Elevated, nonblanching hemorrhages.

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glomerular capillaries, leading to platelet activation and aggregation and the formation of microthrombi.

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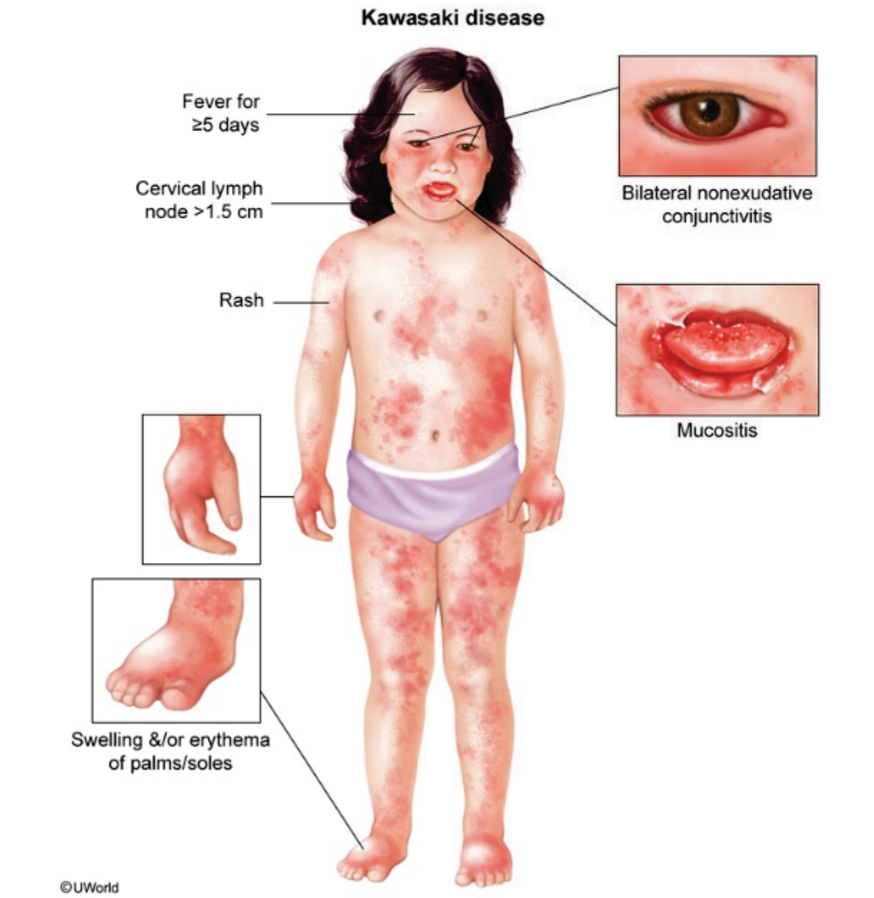
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A 65-year-old woman is treated with gentamicin for an abdominal infection complicated by multidrug-resistant organisms. After a week of treatment, the patient's urine output decreases noticeably, and serum creatinine rises to 2.3 mg/dL. She has no previous kidney disease, and baseline kidney function was normal prior to the initiation of therapy. The patient has remained afebrile for 24 hours. Blood pressure is 130/80 mm Hg and pulse is 80/min. Examination shows moist mucous membranes. There is no rash. Results of urinalysis are as follows:

Protein	+1
White blood cells	1-2/hpf
Red blood cells	none
Microscopy	granular casts

Fractional excretion of sodium is >2%. Histologic examination of the patient's kidneys would most likely show which of the following?

- A. Focal tubular epithelial necrosis
- B. Leukocytic infiltration of the glomerular capillaries
- C. Leukocytic infiltration of the interstitium and tubules
- D. Preservation of normal renal architecture
- E. Replacement of glomeruli with collagen

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Protein	+1
White blood cells	1-2/hpf
Red blood cells	none
Microscopy	granular casts

Fractional excretion of sodium is >2%. Histologic examination of the patient's kidneys would most likely show which of the following?

- ✓ A. Focal tubular epithelial necrosis (70%)
- ✗ B. Leukocytic infiltration of the glomerular capillaries (2%)
- C. Leukocytic infiltration of the interstitium and tubules (22%)
- D. Preservation of normal renal architecture (3%)
- E. Replacement of glomeruli with collagen (0%)

Incorrect
Correct answer
A

70%
Answered correctly

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Explanation

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Acute tubular necrosis due to nephrotoxins	
Common nephrotoxins	• Antibiotics: aminoglycosides (eg, gentamicin), vancomycin • Antivirals: cidofovir, foscarnet • Other: radiographic contrast, cisplatin, heavy metals, heme pigment
Histology	• Tubular epithelial cell necrosis with cell detachment, cast formation & tubular lumen obstruction • Proximal tubules primarily affected
Presentation	• BUN/creatinine ratio <20:1, FENa >2% • Muddy brown (granular) or epithelial cell casts, low urine osmolality • Oliguria or polyuria, ± electrolyte abnormalities
BUN = blood urea nitrogen; **FENa** = fractional excretion of sodium.	

Aminoglycosides (eg, gentamicin, tobramycin) are bactericidal antibiotics that bind to the 30S ribosomal subunit and inhibit protein synthesis. They are commonly used for severe gram-negative infections but carry a significant risk of acute kidney injury. Aminoglycosides are filtered across the glomerulus and concentrate within the proximal renal tubules, where they impair lysosomal function, protein synthesis, and mitochondrial activity, leading to **acute tubular necrosis** (ATN). This is visualized histologically as **focal tubular epithelial necrosis**, often with extensive granular casts that obstruct the tubular lumen and lead to rupture of the basement membrane.

Aminoglycoside-induced kidney injury typically manifests within 1 week of therapy initiation. Due to the high intratubular drug concentrations, ATN can occur despite normal serum drug levels. Proximal tubular dysfunction results in loss of resorptive capacity and **electrolyte wasting** (eg, hypomagnesemia, hypophosphatemia); severe disease can result in Fanconi syndrome (ie, aminoaciduria, glucosuria, uricosuria, phosphaturia). Distal tubular injury may also occur and results in loss of concentrating capacity with polyuria (nonoliguric renal failure). Urinalysis typically demonstrates mild proteinuria with granular or hyaline casts. Consistent with other causes of

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(Choices B and E) Leukocytic infiltration of the glomerular capillaries is seen with vasculitides (eg, granulomatosis with polyangiitis) that cause glomerulonephritis. Chronic glomerulonephritis is characterized by protracted inflammation with collagenous replacement of the glomeruli. However, nephritic diseases typically cause hypertension, hematuria, and red blood cell casts on urinalysis.

(Choice C) Leukocytic infiltration of the interstitium and tubules is seen in acute interstitial nephritis, a common cause of kidney injury that often occurs after introduction of a new drug. However, patients typically have fever and rash, and urinalysis shows pyuria and white blood cell casts.

(Choice D) Patients with prerenal causes of kidney injury (eg, dehydration, blood loss) have normal renal architecture. However, the FENa in prerenal disease is <1%, and the patient would be expected to have signs of hypovolemia (eg, dry mucous membranes).

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(Choice C) Leukocytic infiltration of the interstitium and tubules is seen in acute interstitial nephritis, a common cause of kidney injury that often occurs after introduction of a new drug. However, patients typically have fever and rash, and urinalysis shows pyuria and white blood cell casts.

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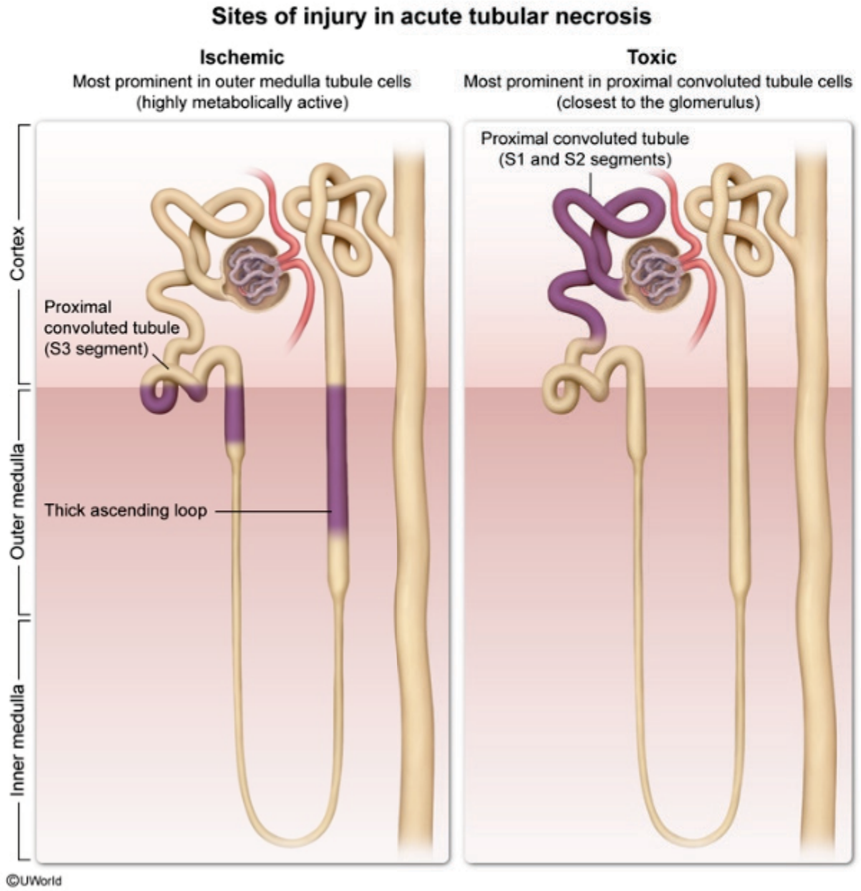
Educational objective:
Aminoglycosides are filtered across the glomerulus and concentrate in the renal tubules, leading to proximal tubular injury and acute tubular necrosis. This is visualized histologically as focal tubular epithelial necrosis, often with extensive granular casts that obstruct the tubular lumen and lead to rupture of the basement membrane.

Pathology	Renal, Urinary Systems & Electrolytes	Aminoglycoside

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Histology	lumen obstruction

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(Choice C) Leukocytic infiltration of the interstitium and tubules is seen in acute interstitial nephritis, a common

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A 23-year-old man comes to the office due to 3 weeks of malaise and fatigue. He says, "I've been sick with the flu for the last 3 weeks. I don't know why I'm not getting better." The patient also has profound fatigue causing difficulty with day-to-day activities. His temperature is 38.4 C (101.2 F). Cardiac auscultation reveals an apical holosystolic murmur radiating to the axilla, which was not heard during previous office visits. Laboratory evaluation shows serum creatinine of 2.3 mg/dL. Mild proteinuria and microscopic hematuria with red cell casts are present on urinalysis. Which of the following is the most likely pathogenesis of this patient's renal findings?

- A. Anti-glomerular basement membrane antibodies
- B. Circulating immune complex-mediated injury
- C. Endotoxin-induced renal tubular injury
- D. Hematogenous metastatic infection focus
- E. Thromboembolic event

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- A. Anti-glomerular basement membrane antibodies (8%)
- ✓ B. Circulating immune complex-mediated injury (75%)
- C. Endotoxin-induced renal tubular injury (6%)
- D. Hematogenous metastatic infection focus (5%)
- E. Thromboembolic event (4%)

Correct

75% Answered correctly

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Explanation

This young patient's constitutional (flulike) symptoms, fever, and a new systolic murmur suggest **infective endocarditis** (IE). Elevated serum creatinine with hematuria and proteinuria further suggest renal insufficiency due to a nephritic syndrome. In some patients, IE may be complicated by deposition of circulating immune complexes in the glomerular capillary wall, resulting in glomerulonephritis. This can be seen as capillary wall thickening with subendothelial and subepithelial deposit formation. Hypercellularity similar to that seen in poststreptococcal glomerulonephritis or membranoproliferative glomerulonephritis is revealed on light microscopy

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Explanation

This young patient's constitutional (flulike) symptoms, fever, and a new systolic murmur suggest **infective endocarditis** (IE). Elevated serum creatinine with hematuria and proteinuria further suggest renal insufficiency due to a nephritic syndrome. In some patients, IE may be complicated by deposition of circulating immune complexes in the glomerular capillary wall, resulting in glomerulonephritis. This can be seen as capillary wall thickening with subendothelial and subepithelial deposit formation. Hypercellularity similar to that seen in poststreptococcal glomerulonephritis or membranoproliferative glomerulonephritis is revealed on light microscopy.

(Choice A) Anti-glomerular basement membrane (anti-GBM) autoantibodies can also cause an acute nephritic syndrome. However, these antibodies do not affect cardiac tissues and would not cause a new cardiac murmur. Anti-GBM antibodies may target the pulmonary alveolar basement membrane, causing hemoptysis (Goodpasture syndrome).

(Choice C) IE is rarely caused by gram-negative organisms, the producers of endotoxin. Furthermore, endotoxin production can cause acute tubular necrosis as part of sepsis but is unlikely to cause glomerulonephritis.

(Choices D and E) Emboli from infected endocardial vegetations may metastasize via the hematogenous route to cause infarcts in the brain, kidneys, myocardium, and other tissues (eg, Janeway lesions on palms and soles). Emboli are usually small and do not cause acute renal failure. Renal failure may be seen if the infectious embolic focus develops into an abscess or the embolus is large enough to cause a sizeable infarct. However, both renal infarct and abscess present with flank pain.

Educational objective:
The most likely cause of fever and fatigue with new-onset cardiac murmur is infective endocarditis (IE). Diffuse, proliferative glomerulonephritis secondary to circulating immune complex deposition may complicate IE and can result in acute renal insufficiency.

Pathology Renal, Urinary Systems & Electrolytes Endocarditis

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A 68-year-old male presents to your office complaining of difficulty urinating. His past medical history is significant for prostate cancer treated with radiation therapy one year ago. Ultrasonography reveals bilateral dilation of the ureters and renal calyces. If related to the previous therapy, which of the following is the most likely cause of this patient's current condition?

- A. Granuloma formation
- B. Radiation mucositis
- C. Fibrosis
- D. Mucosal ulceration
- E. Mucosal hyperplasia

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- A. Granuloma formation (1%)
- ✗ B. Radiation mucositis (9%)
- ✓ C. Fibrosis (75%)
- D. Mucosal ulceration (1%)
- E. Mucosal hyperplasia (12%)

Incorrect
Correct answer
C

75%
Answered correctly

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Explanation

Radiotherapy has applications as primary, adjuvant, or more commonly palliative therapy for many types of cancer. Tumor sensitivity to radiation depends on the rate of cell turnover, with rapidly growing tumors being more sensitive. In the same way, rapidly dividing normal body tissues such as blood cell precursors, epithelial surfaces in the skin, GI tract, and urinary tract, and the gonads (gametes) are also at risk for damage. **Fibrosis** and **strictures** due to diffuse scarring of the damaged tissues often occurs as a late complication of radiotherapy for prostate cancer, and may lead to **obstructive uropathy**.

(Choice A) Granuloma formation occurs in diseases such as sarcoidosis (sterile, non-caseating granulomas),

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Radiotherapy has applications as primary, adjuvant, or more commonly palliative therapy for many types of cancer. Tumor sensitivity to radiation depends on the rate of cell turnover, with rapidly growing tumors being more sensitive. In the same way, rapidly dividing normal body tissues such as blood cell precursors, epithelial surfaces in the skin, GI tract, and urinary tract, and the gonads (gametes) are also at risk for damage. **Fibrosis** and **strictures** due to diffuse scarring of the damaged tissues often occurs as a late complication of radiotherapy for prostate cancer, and may lead to **obstructive uropathy**.

(Choice A) Granuloma formation occurs in diseases such as sarcoidosis (sterile, non-caseating granulomas), tuberculosis (caseating necrosis with Langhans giant cells and acid-fast bacilli), and in foreign body reactions (foreign body giant cells, sometimes surrounding an identifiable foreign body).

(Choices B & D) Radiation mucositis and mucosal ulceration occur after radiotherapy for gastrointestinal tumors and head and neck malignancies. These early effects resolve soon after discontinuation of treatment.

(Choice E) Mucosal hyperplasia is seen in patients treated with phenytoin (gingivae) and can also be seen in states where there is hypersecretion of a hormone that is trophic for a mucosal surface as occurs in the gastric mucosa with gastrinoma.

Educational objective:
Fibrosis and strictures are late effects of radiation therapy. Radiotherapy for prostate cancer may lead to urethral fibrosis and result in obstructive uropathy.

Pathology	Renal, Urinary Systems & Electrolytes	Prostate cancer
Subject	System	Topic

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A 56-year-old woman comes to the office due to generalized muscle weakness and muscle cramps. Medical history is significant for Sjögren syndrome, but she takes no medications. Physical examination shows mild muscle weakness. Laboratory results are as follows:

Serum potassium	decreased
Serum bicarbonate	decreased
Serum anion gap	normal
Urinary ammonium excretion	decreased

Which of the following best explains the laboratory findings in this patient?

- A. Impaired distal tubule acid secretion
- B. Increased proximal tubule bicarbonate reabsorption
- C. Increased production of systemic endogenous acids
- D. Renal compensation for alveolar hypoventilation
- E. Resistance of distal tubule to aldosterone effect

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Incorrect
Correct answer
A

Collecting Statistics

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Explanation

Renal tubular acidosis

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Renal tubular acidosis			
Type	**1 (distal)**	**2 (proximal)**	**4**
Defect	↓ H^+ secretion from alpha-intercalated cells	↓ HCO_3^- reabsorption	↓ Aldosterone, aldosterone resistance (principal cells)
Associations	• Autoimmune • Hereditary (children) • Calcium phosphate stones	• Fanconi syndrome (glycosuria, phosphaturia, aminoaciduria) • Carbonic anhydrase inhibitors (eg, acetazolamide)	• Diabetic nephropathy (↓ renin activity) • ACE inhibitors, ARBs
Serum K^+	Low	Low	High
Urine pH	>5.5	<5.5	<5.5
ARB = angiotensin II receptor blocker.			

The kidneys can excrete a limited amount of acid as free H^+; therefore, most H^+ is excreted in the form of ammonium (NH_4^+). This patient with hypokalemia, nonanion gap metabolic acidosis (ie, decreased serum bicarbonate [HCO_3^-]), and decreased urinary ammonium excretion most likely has **type 1 renal tubular acidosis** (RTA), a potential complication of autoimmune disease (eg, Sjögren's syndrome) involving **impaired acid excretion** (eg, H^+ ATPase dysfunction) by alpha-intercalated cells of the **distal tubule**.

Type 1 RTA creates a **nonanion gap metabolic acidosis**, as do all types of RTA, due to retention of H^+ and a net loss of HCO_3^-. Impaired distal tubular acid secretion also leads to increased K^+ excretion and consequent **hypokalemia**. Urine **pH is >5.5** due to markedly impaired ability to acidify the urine, and muscle weakness may develop due to hypokalemia. In addition, metabolic acidosis can leach calcium from bones, causing osteomalacia and increasing urinary calcium excretion. Compared to other types of RTA, type 1 carries particular susceptibility

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(Choice B) Impaired (not increased) proximal tubule HCO_3^- reabsorption is the cause of type 2 RTA. As with type 1, nonanion gap metabolic acidosis and hypokalemia develop, but urine pH is more acidic (ie, <5.5) because intact distal H^+ excretion compensates somewhat for the impaired proximal HCO_3^- reabsorption (ie, urine ammonium excretion is normal).

(Choice C) Increased production of systemic endogenous acids (eg, lactic acidosis, diabetic ketoacidosis) creates an anion gap metabolic acidosis. High urinary ammonium excretion is expected (assuming the kidneys are functioning normally) as the kidneys try to excrete excess acid.

(Choice D) Alveolar hypoventilation causes respiratory acidosis. In response, the kidneys increase ammonium excretion to increase serum HCO_3^- and create a compensatory metabolic alkalosis.

(Choice E) Resistance of the distal tubule to aldosterone is the cause of type 4 RTA. It most commonly occurs with diabetic nephropathy and is characterized by reduced urinary acid excretion and nonanion gap metabolic acidosis. However, in contrast to type 1 and type 2, hyperkalemia is expected.

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Educational objective:

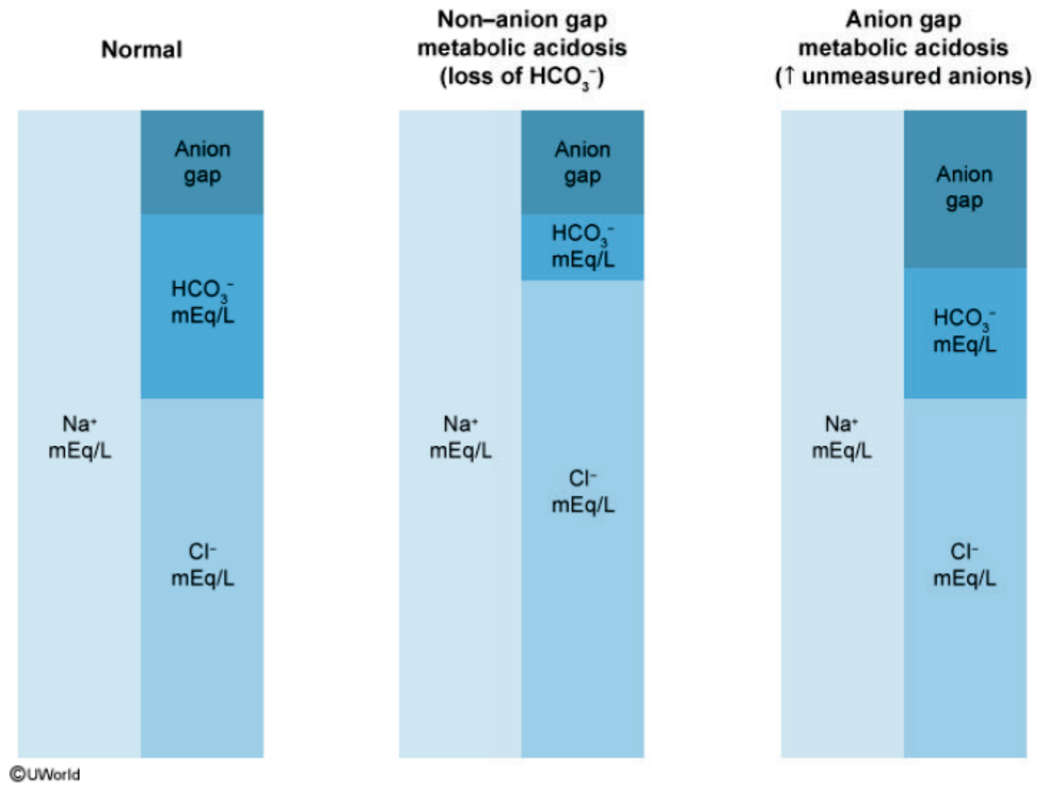
Type 1 renal tubular acidosis results from impaired distal tubular excretion of H^+ (in the form of ammonium [NH_4^+]). Patients typically have nonanion gap metabolic acidosis, hypokalemia, and markedly impaired ability to acidify the urine with urine pH >5.5.

References

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	stones	(eg, acetazolamide)
		• ACE inhibitors, ARBs

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Urine pH	>5.5	<5.5	<5.5

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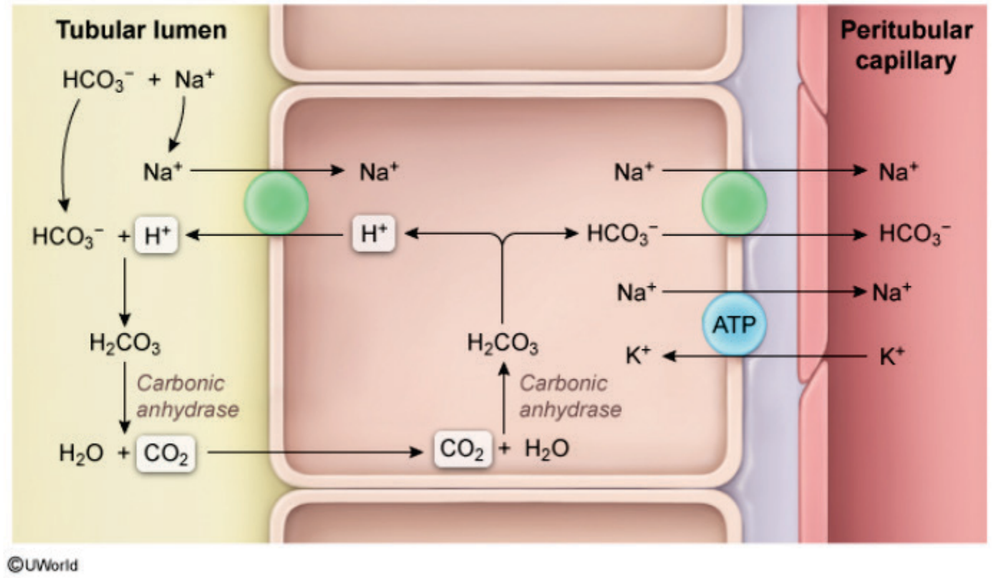
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excretion to increase serum HCO_3^- and create a compensatory metabolic alkalosis.

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(RTA), a potential complication of autoimmune disease (eg, Sjögren's syndrome) involving **impaired acid**

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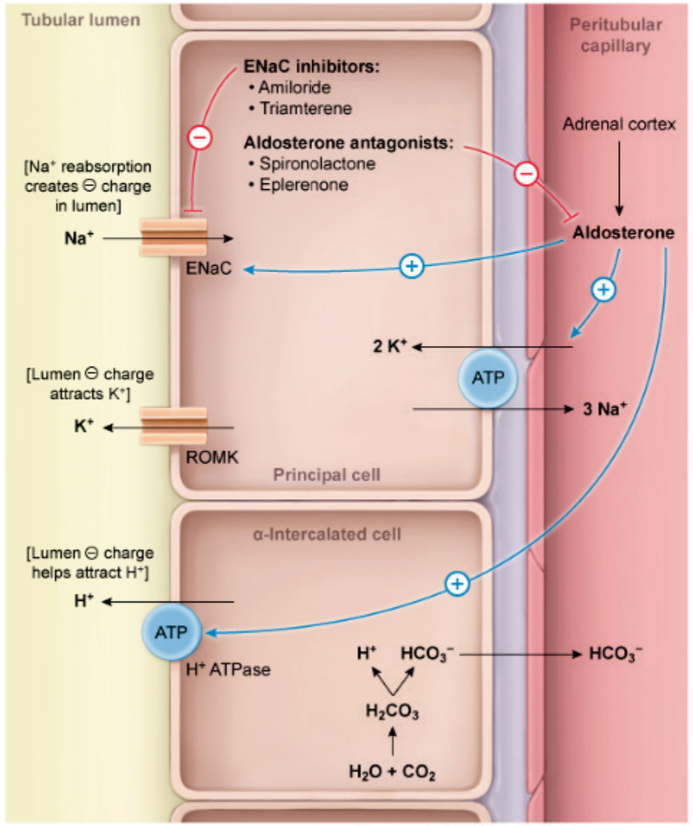
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Type 1 renal tubular acidosis results from impaired distal tubular excretion of H^+ (in the form of ammonium [NH_4^+]).

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Action of aldosterone in the collecting duct of the nephron



ENaC = epithelial sodium channel; **ROMK** = renal outer medullary potassium channel. ©UWorld

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